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TUMORS OF THE PALATE (BENIGN AND MALIGNANT)

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The palate, hard and soft, gives rise to a varied group of tumors—epidermoid carcinoma, adenocarcinoma and benign mixed tumors. Melanoma, lymphosarcoma and myosarcoma occur only rarely in this structure. In most parts of the oral cavity malignant tumors can be reasonably separated from benign tumors. Such definite separation is impossible in the palate, where there is a gradual transition in the cellularity of benign tumors into cancer. The title of this report is therefore "Tumors [rather than Cancer] of the Palate."

The present report is based on a series of all patients with neoplasms of the hard and soft palates admitted to the Memorial Hospital for the Treatment of Cancer and Allied Diseases from 1929 to 1936, inclusive. Of those with malignant tumors, none have been excluded because of the advanced stage of the disease.

DEFINITION

The term "tumors of the palate" should be limited to growths arising on the inferior, or oral, surface of the hard and soft palates (roof of the mouth). The upper surface of the hard and soft palates forms the floor of the nasal cavity and of the nasopharynx, respectively, and growths which arise on this surface are classified as nasal cavity or nasopharyngeal, rather than palatal, tumors.

In the English language there is no term to differentiate the bone of the hard palate from the overlying soft tissue, although in German *Gaumen* designates the soft tissues covering both the palate and the alveolar processes. Since growths of the bony hard palate are extremely rare, the lack of such a term in English causes no confusion. In the present discussion the terms "hard palate" and "soft palate" will be used to refer only to the soft tissues, in which practically all palatal tumors arise.

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The palate is the site of origin of a greater percentage of benign "mixed" tumors of salivary gland type than is any other structure in the head and neck except the parotid salivary gland, as will be discussed in more detail. These tumors are almost identical in histologic nature and in clinical course with mixed tumors of the parotid gland. Wherever they arise, it is sometimes difficult, both histologically and clinically, to distinguish between cellular benign mixed tumor and cancer. It is obvious that some benign mixed tumors after varying periods of quiescence may change in character, certain elements becoming frankly malignant (carcinomatous), and pursue a malignant course.

The term "cancer of the palate" includes two main histologic groups: (1) epidermoid carcinoma arising in the squamous epithelium and (2) the adenoid tumors arising in minor salivary and mucous glands, consisting mainly of adenocarcinomas. For purposes of statistical analysis it is essential that these histologic groups be considered individually as well as collectively, since they differ markedly in etiology, incidence, clinical course and response to treatment.

ANATOMY OF THE PALATE

The palate, which forms the roof of the mouth, is divided anatomically into the hard palate anteriorly and the soft palate posteriorly. The bony hard palate consists of the palatal processes of the maxilla anteriorly fused with the horizontal parts of the palate bones posteriorly, this bony structure being covered on its inferior surface by periosteum, a layer of fibrous tissue and submucosa, and finally mucous membrane. In the anterior portion of the hard palate these soft tissues present a number of transverse ridges, the plicae palatinae, which are strongly developed in carnivora.

The soft palate is attached anteriorly to the posterior margin of the hard palate and is continuous laterally with the supratonsillar fossae and the tonsillar pillars. The latter curve upward and backward to form the posterior free edge of the soft palate, in the center of which is the uvula. The soft palate (5 to 7 mm. in thickness) consists of a strong fibrous sheet covering the palatine aponeurosis, in which are attached several muscles (musculi pharyngopalatini, uvulae, levatores veli palatini, tensores veli palatini and glossopalatini) covered on both upper and lower surfaces by stratified squamous epithelium over a submucosa of relatively loose areolar tissue. By virtue of its intrinsic musculature, the soft palate performs an important function during the act of swallowing —that is, closure of the opening into the nasopharynx—and invasion of this musculature by cancer or erosion of the palate by a growth is attended by marked disability both in swallowing and in speaking.

The submucosa of both the hard and the soft palate contains a great number of racemose and mucous glands; these glandular structures

increase in number toward the posterior margin of the soft palate, so that they make up most of the body of the uvula. The abundance of these glandular structures accounts for the frequency of adenoid tumors in the palate.

The blood supply of the palate consists of a number of small arterial branches (descending palatine, nasal septal, ascending palatine and others) which arise from the internal maxillary, external maxillary, ascending pharyngeal and lingual arteries. None of the branches in the palate itself is large enough to permit excessive hemorrhage. Serious bleeding in palatal cancer occurs almost always from erosion of larger arteries in adjacent structures.

ANATOMY OF THE LYMPHATICS OF THE PALATE

The finer lymphatics of the hard and soft palates are continuous with each other and with those of the gums and of the palatine tonsils. The finer capillary network gives origin to collecting trunks which pass backward to reach the retromolar triangle and from this point follow three different routes to reach the internal jugular chain, the submaxillary nodes and the retropharyngeal nodes, respectively. From these several groups of nodes the efferent lymph drainage passes into the middle and lower nodes of the internal jugular chain.

According to anatomists,[1] the main lymphatic pathway from the retromolar triangle is downward along the anterior border of the ascending ramus, mesial to the horizontal ramus and the submaxillary salivary gland, and then to the inner side of the posterior belly of the digastric muscle to the subdigastric lymph nodes of the internal jugular chain. The behavior of metastases in the present series proves the predominance of the latter pathway, since in over 75 per cent of the cases with metastasis the subdigastric nodes were the first to be involved.

The anterior lymphatic trunks of the palate first pass backward over the upper gums posterior to the third molar tooth and immediately penetrate deeply into the tissues of the cheek, where they join the lymphatics of the buccal mucosa, pierce the buccinator muscle and descend along the course of the external maxillary blood vessels to the prevascular and retrovascular lymph nodes of the submaxillary group. The anterior pathway to the submaxillary nodes is said by anatomists to be inconstant, a view not fully supported by the observations at the Memorial Hospital, since in a considerable number of the cases in the present series (16 per cent of those with metastases) the first node involved was in the submaxillary group.

1. Rouvière, H.: Anatomy of the Human Lymphatic System, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938. Sassier, P.: Lymphatiques de la voute palatine, du voie du palais et de la luette, Ann. d'anat. path. **4**:933, 1927.

Anatomists refer to a third and rare pathway by which a few collecting trunks pierce the pharyngopalatinus muscle and the superior constrictor of the pharynx to enter the retropharyngeal space and empty into the lateral retropharyngeal node; but at the Memorial Hospital my associates and I have never been able to demonstrate metastasis to the retropharyngeal nodes from cancer of the palate.

ETIOLOGY

General Incidence.—According to the admission records of the Memorial Hospital, malignant tumors of the palate (excluding benign mixed tumors) make up about 8 per cent of all oral cancer, about 5 per cent of all cancer of the upper respiratory and alimentary tracts and about 2 per cent of all human cancer. The incidence ratio of malignant growths to benign mixed tumors in the palate is 12 to 1.

Most reports in the literature agree that the palate is the most frequent site of origin of adenoid tumors (adenocarcinomas and mixed tumors) in the oral cavity. Watson [2] in 1935 reported a series of 46 adenocarcinomas of the oral cavity from the Memorial Hospital and found that over 50 per cent arose in the palate. Abshier [3] stated that with the exception of the parotid and salivary glands the palate is the most frequent site of mixed tumors. In the New and Childrey [4] series of 74 cases of "adenocarcinoma of mixed tumor type" in the tonsil and the pharynx (including the palate) 56 per cent of the tumors were in the palate. In the present series of 103 palatal tumors, 24 (24 per cent) were of the adenoid type, a figure less than that reported by Ahlbom,[5] who stated that of 62 palatal tumors treated at Radiumhemmet between 1921 and 1932, 35 per cent were of the mucous and salivary gland type.

Many authors erroneously consider mixed salivary gland tumors of the palate to be extremely rare. Sonnenschein [6] in 1929 was able to collect less than 50 cases from a complete survey of the literature, and

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2. Watson, W. L.: Adenocarcinoma of the Oral Cavity, Am. J. Roentgenol. **34**:53, 1935. Watson, W. L., and Pool, J. L.: Cancer of the Thyroid, Surg., Gynec. & Obst. **70**:1037, 1940.

3. Abshier, A. B.: Mixed Tumors of the Palate, Arch. Dermat. & Syph. **32**: 622 (Oct.) 1935.

4. New, G. B., and Childrey, J. H.: Tumors of the Tonsil and Pharynx: II. Adenocarcinomas of the Mixed Tumor Type, Arch. Otolaryng. **14**:699 (Dec.) 1931.

5. Ahlbom, H. E.: Mucous- and Salivary-Gland Tumors, Acta radiol., 1935, supp. 23, p. 1.

6. Sonnenschein, R.: "Mixed" Tumors Occurring in the Soft Palate with Reports of Two Cases and a Survey of the Recent Literature, Tr. Am. Laryng. A. **51**:235, 1929.

in 1937 Rhoads and Mecray [7] stated that only 12 new cases had been recorded since Sonnenschein's report. The paucity of reports in the literature gives a false idea of the incidence of this tumor, which is undoubtedly more frequent than the figures indicate. The long duration with few symptoms for the benign and even for some of the malignant tumors is undramatic, and in the older age group the patients are likely to die of other causes rather than of their primary tumors. When systemic metastasis occurs long after the control of the primary lesion in a case of adenocarcinoma, it is probable that the association with the former palatal tumor is often not realized.

Age Incidence.—The average age on admission in the present series of 103 cases of palatal tumors (benign and malignant) was 57 years, which is about the same as that in cases of intraoral cancer in general. There was a noteworthy difference in the mean ages of patients with epidermoid carcinoma (61 years), with adenocarcinoma (48 years) and with benign mixed tumors (37 years). This difference becomes even more apparent when the average ages at the beginning of symptoms are calculated. The duration before admission in cases of epidermoid carcinoma (seven months) was relatively short compared with the duration (about three years) in cases of the adenoid group (adenocarcinoma and mixed tumors). According to the histories of the 2 oldest patients with mixed tumors the duration of the lesions was twenty-five and nine years, respectively. The mean ages of the patients at the onset of symptoms were: epidermoid carcinoma, 60 years; adenocarcinoma, 46 years; mixed tumors, 31 years. In brief, epidermoid carcinoma of the palate is a disease of old age, while adenoid tumors occur mainly in the young or middle aged and almost always before the age of 45. In the series of cases of intraoral adenocarcinoma from the Memorial Hospital analyzed by Watson, the average age was 49 years; and New and Childrey [4] in 74 cases of adenocarcinoma of the pharynx (including the palate) and the tonsil found the average age to be 45.5 years. In Ahlbom's [5] report the age incidence is calculated on the combined groups with parotid, submaxillary and mucous membrane tumors, but the general trend agrees with the aforementioned figures, that is, the average age of patients with benign and semimalignant mucous and salivary gland tumors is given as 43 years, while for patients with malignant tumors the corresponding age was 52 years. Ahlbom also called attention to the significance of calculations based on the time of the beginning of symptoms in these groups of cases.

In the records of the Memorial Hospital there are 2 cases of myosarcoma of the palate, both the patients being female children, 7 and 9 years, respectively. One of these cases is included in the present series.

7. Rhoads, J. E., and Mecray, P. M., Jr.: Recurrence in Mixed Tumors of the Soft Palate, Am. J. M. Sc. **193**:389, 1937.

Sex Incidence.—There was a noteworthy difference in sex distribution between the epidermoid and the adenoid tumors of the palate. For epidermoid carcinoma in this area the sex distribution (90 per cent in males; 10 per cent in females) was about the same as for epidermoid carcinoma of the oral cavity in general. The adenoid tumors of the palate affected females (58 per cent) more often than males (42 per cent). Watson found that adenocarcinoma of the oral cavity in general was distributed about equally between the two sexes.

There is not complete agreement in the literature on the sex incidence of mucous and salivary gland tumors. Some authors [8] have reported different degrees of predominance in men. Others [9] have reported about an equal incidence in the two sexes. Even an equal distribution between the sexes would be of significance, since other tumors in this area (epidermoid group) are found predominantly in males (80 to 95 per cent). In this connection it might be of interest to mention that according to the records of the Memorial Hospital certain other forms of glandular cancer are found preponderantly in females, namely, cancer of the parotid gland (60 per cent), adenocarcinoma of the skin (60 per cent) and cancer of the thyroid gland (70 per cent). The most definite exceptions to this rule are cancer of the stomach (75 per cent in males) and cancer of the rectum (66 per cent in males).

The female preponderance (58 per cent) of adenoid tumors of the palate in the present series may be coincidental only, since the difference is not great and the series is small. This figure is identical, however, with that obtained by Ahlbom [5] in 254 cases of mucous and salivary gland tumors, including parotid and submaxillary salivary gland tumors. Ahlbom found an even greater female preponderance (65 per cent) in 130 patients with benign and semimalignant tumors alone. Kennon [10]

8. Heineke, H.: Bösartige Geschwülste der Speicheldrüsen, in Zweifel, P. P., and Payr, E.: Die Klinik der bösartigen Geschwülste, Leipzig, S. Herzel, 1924, vol. 1, p. 760. Nyström, G.: Kräftsjukdomarne i Sverige, Stockholm, Svenska Tryckeriaktiebolaget, 1922; cited by Ahlbom.[5] Pack, G. T., and LeFevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, J. Cancer Research **14**:167, 1930. Rodriguez, L.: Contribution à l'étude du sarcome pur de la parotide, Thesis, Paris, no. 240, 1890. New and Childrey.[4]

9. Benedict, E. B., and Meigs, J. V.: Tumors of the Parotid Gland: Study of Two Hundred and Twenty-Five Cases with Complete End Results in Eighty Cases, Surg., Gynec. & Obst. **51**:626, 1930. Schreiner, B. F., and Mattick, W. L.: Tumors of the Salivary Glands Based on a Study of Sixty-Six Cases, Am. J. Roentgenol. **21**:541, 1929. Stein, I., and Geschickter, C. F.: Tumors of the Parotid Gland, Arch. Surg. **28**:491 (March) 1934. Stöhr, F., and Risak, E.: Zur Klinik und Anatomie der Parotisgeschwülste, Arch. f. klin. Chir. **143**:609, 1926. Sonnenschein.[6]

10. Kennon, R.: Tumours of the Salivary Glands with Their After-History, Brit. J. Surg. **9**:76, 1921.

and Hintze [11] also reported a female preponderance (66 per cent) for parotid mixed tumors. Although the voluminous statistical material is sometimes contradictory, it is significant that among those authors who have subjected their material to the most careful analysis the trend toward reporting a higher incidence in females is rather definite.

Position of the Growth.—Neoplasms occur more often in the soft than in the hard palate. The majority of epidermoid carcinomas occur on the soft palate, and the posterior edge of this structure is more often involved than any other part. Epidermoid carcinomas tend to occur on the soft palate (73 per cent) more often than on the hard (27 per cent), while with mucous and salivary gland tumors the ratio is reversed (43 per cent in the soft palate and 57 per cent in the hard). Ahlbom [6] found the occurrence of salivary gland tumors to be higher in the hard palate (16 cases) than in the soft (6 cases). Epidermoid carcinomas are fairly well distributed between the two sides and the center of the palate, whereas adenocarcinomas practically always arise on one side or the other of the midline. In the present series none appeared directly in the midline. The right and left sides were involved in about equal percentages of cases.

Causative Factors.—After a consideration of the etiology, the morbid anatomy and the clinical course it becomes obvious that different factors must operate to produce, respectively, epidermoid and adenoid tumors of the palate. Epidermoid carcinoma arises in patients of the older age group, in whom the mucous membranes have suffered the characteristic degenerative changes of the aging process. In patients with tumor of this type there is the usual high percentage of precancerous changes in the oral mucous membranes (leukoplakia, chronic glossitis, atrophy) which result from extraneous irritants. As with all forms of epidermoid cancer of the mucous membranes or skin, the sex distribution is predominantly male (85 to 95 per cent). On the other hand, adenoid tumors (malignant and benign) occur about fifteen years earlier; mucous membrane changes due to extraneous irritants are uncommon, and the sex distribution is preponderantly female.

In the epidermoid group of the present series there was evidence of subacute or chronic irritation of the mucous membrane (leukoplakia, glossitis, atrophy) in about 35 per cent of the cases, which approaches the incidence of such abnormalities in the general group of intraoral cancer. In the adenoid group there was no evidence of subacute or chronic irritation in any of the cases. It is more difficult with palatal cancer than with the average intraoral growth to demonstrate (either by history or by objective findings) the influence of the more common

11. Hintze, A.: Gutartige und bösartige Parotisgeschwülste und ihre Heilungsmöglichkeiten, Arch. f. klin. Chir. **180**:606, 1934.

forms of chronic irritation, namely, syphilis, tobacco and trauma from dentures. The same is true of the stomatitis following dietary deficiencies, mainly avitaminosis B, of which little evidence was noted in the present series.

Leukoplakia.—Any form of long-standing chronic irritation of mucous membranes may result in leukoplakia or cancer or both in the same patient. Leukoplakia was specifically noted in 27 per cent of the patients with epidermoid carcinoma in the present series. It was absent in all of the group with adenoid tumors.

Syphilis.—In the present series Wassermann tests were made in 58 cases, and all gave negative reactions. Although this negative finding is probably accidental, it is nevertheless a strong indication that syphilis plays no significant role in the etiology of palatal cancer. In contrast, about 30 per cent of the patients with cancer of the tongue in the Memorial Hospital have positive Wassermann reactions. The degenerative changes in the oral mucous membrane in chronic syphilis (leukoplakia and atrophy) are most frequent and marked on the tongue but in most cases spread also to the gums, the cheeks and the palate.

Tobacco.—In heavy pipe smokers there is a tendency toward epithelization of the palatal mucosa where the stream of hot smoke strikes the roof of the mouth. This change differs somewhat in appearance from the average leukoplakia of the oral cavity, that is, the palatal mucosa is greatly thickened and often presents a variable number of small to large round elevated papillary projections, somewhat resembling the circumvallate papillae in appearance. If one of these is removed when small, it is difficult to prove histologically anything further than chronic inflammatory changes, but larger lesions usually show papillomatous overgrowth of the epithelium. Although common in pipe smokers, such changes in the palatal mucosa are rarely seen in association with cancer, and there is little statistical evidence to indicate that they have any great importance from the standpoint of cancerigenesis. In the present series about 60 per cent of the patients reported past or present use of tobacco—an incidence slightly below that of the tobacco habit in cases of intraoral cancer in general (70 to 75 per cent). Mucous membrane changes seldom result in the soft palate from the tobacco habit, except in heavy cigar smokers (those who smoke fifteen to twenty a day), in whom the soft palate and the base of the tongue become deep red and congested with marked hypertrophy of lymphoid tissue. Cancer of the base of the tongue or soft palate associated with heavy cigar smoking (an expensive habit) has been termed "rich man's cancer."

Dental Trauma.—Dental diseases and defects, including sharp or worn teeth, should have little significance in the etiology of palatal cancer,

since the teeth do not come into contact with the palate. Of the entire group, about one third of the patients were edentulous in the upper jaw, and only 4 believed that the upper dental plate had irritated the palate. It would be logical to suppose that when an upper dental plate completely covering the gums and the hard palate is kept in place constantly and not removed for cleansing, there would be a retention of partly decomposed secretions and debris between the plate and the palate and that such an accumulation would frequently produce sufficient chronic irritation to cause cancer. It is significant that such an association is rarely found. None occurred in the present series. Recently, however, I have observed epidermoid carcinoma at the junction of the hard and soft palates in a patient who had worn the same full upper dental plate for fifteen years. Retention of this plate had been obtained by undercutting, and the device was so difficult to remove that it was left in place; the patient had gone to his dentist at intervals of not less than six months,

TABLE 1.—*Duration of Symptoms and Size of Lesion in 101 Cases of Tumor of the Palate*

Histologic Type	Duration of Symptoms Before Admission	Av. Size of Lesion on Admission (Cm.)
Epidermoid carcinoma	7 mo.	3.5
Adenocarcinoma	27 mo.	3.0
Benign mixed tumors	5 yr.	4.5

and often more than a year, for cleaning and reinsertion. In this instance the growth had occurred not directly under the plate but at its posterior margin.

SYMPTOMS, MORBID ANATOMY AND CLINICAL COURSE

The three main histologic varieties of palatal cancer—epidermoid carcinoma, adenocarcinoma and mixed tumor—differ in symptoms, morbid anatomy and clinical course, and will therefore be considered separately from these standpoints. The variations in duration of symptoms and size of lesion on admission are given in table 1. The relatively short average duration (seven months) of epidermoid carcinoma and the large average size on admission (3.5 cm.) indicate that this tumor grows rapidly as compared with the adenoid group. The average duration of symptoms of adenocarcinoma is about four times as long (twenty-seven months) as that of epidermoid carcinoma, and the average size of the former tumor (3 cm.) is somewhat smaller. New and Childrey reported an average size of adenocarcinomas of the oral cavity of 5 cm. One of the most outstanding characteristics of mixed tumors is the long duration (average, over five years in the present series; twenty-five years

in 1 case); another is the slow, symptomless growth which permits these tumors to reach an unusually large average size (4.5 cm.).

The hard palate is in almost constant contact with the tactually sensitive tip and dorsum of the tongue, so that irregularities of the palate cannot long escape the attention of an alert patient. The base of the tongue, which lies in contact with the soft palate, does not possess tactile sensation, but ulcerated lesions of the soft palate are more likely to be painful in the early stages, since this structure is functionally mobile during swallowing.

Epidermoid Carcinoma of the Palate.—In the present series the most common site of origin of epidermoid carcinoma was in or near the free edge of the soft palate (73 per cent) with about 22 per cent of the tumors

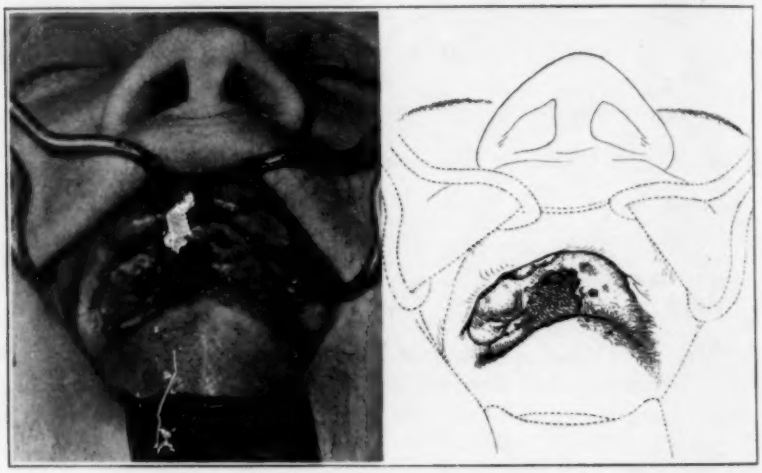

Fig. 1.—Epidermoid carcinoma of the palate. Epidermoid carcinoma of the palate is likely to be a flat, thin, ulcerated, granular lesion; adenocarcinoma in this area is usually raised, ovoid, moundlike and only partly ulcerated; benign mixed tumors are rarely ulcerated.

originating in the hard palate and about 5 per cent at the junction between the two. From the appearance of the earlier lesions it seems that the growth begins as a small superficial granular ulcer with raised rolled edges which tends to fungate from rather than to infiltrate the mucous membrane (fig. 1).

There are apparently few subjective symptoms in the early stages, since in the present series the average diameter of the primary lesions on admission was about 3.5 cm. The most common first symptom (in over 40 per cent of the cases) was the discovery of the lesion itself as a painless irregularity of the mucous membrane. When the growth arises

in the hard palate, there is no interference in function until it is far advanced and infected; then an upper dental plate may become ill fitting or mastication may be painful. As the growth extends, the periosteum overlying the hard palate resists invasion for a time, so that erosion of bone is always a late complication. In the present series it had occurred before admission in only 2 cases, in 1 of which there was perforation into the nasal cavity. Less than 10 per cent of the patients complained of pain or discomfort as the first symptom; it was more common in the soft palate than in the hard.

When the growth arises in the soft palate, pain on swallowing occurs when there is sufficient erosion to permit of deep infection and inflammation of this movable structure. With invasion of the intrinsic musculature there is limitation of the normal elasticity and range of motion of the soft palate, which when functioning normally rises to close off the opening into the nasopharynx during the act of swallowing. As a result of this interference with function, liquid ingesta tend to enter the nasal cavity and to be expelled through the nose. This complication becomes more severe with actual erosion through the soft palate. Normal speech is also altered by any disability of the soft palate.

If uncontrolled locally, epidermoid carcinoma of the palate finally invades and erodes the palate widely, extending onto the pharyngeal walls and the mucosa of the cheeks, producing trismus of the jaws, intractable pain and sepsis. In the unsuccessfully treated patients in the present series, death resulted with about equal frequency from local recurrences at the primary site and from metastasis to the neck or systemic metastasis.

Adenoid Tumors of the Palate.—Adenocarcinoma and mixed tumors of the palate have the same histogenesis, and there is little to distinguish them from the standpoint of clinical appearance and morbid anatomy. They both exhibit the same slowly growing, sharply delimited ovoid submucous mass. They differ mainly in that adenocarcinoma has a slightly more rapid rate of growth and may eventually metastasize, while mixed tumors grow more slowly and do not disseminate beyond the point of origin. Except in their more advanced stages, these two forms of palatal tumors can be differentiated only by histologic examination. On the other hand, the adenoid tumors can be differentiated readily from epidermoid carcinomas of this structure by clinical appearance alone.

In the present series adenoid tumors occurred with slightly greater frequency in the hard palate (11 cases, 57 per cent) than in the soft (8 cases, 43 per cent); in 4 cases the growth appeared to arise at the junction between the two. Theoretically this proportion should be reversed, since the racemose mucous glands are more numerous in the soft palate than in the hard. The relative proportion of adenocarcinomas

and mixed tumors was about the same in all parts of the palate. Since these tumors always grow slowly, there has been adequate opportunity in the Head and Neck Clinic of the Memorial Hospital to observe them in all stages of development. In some cases they may be diagnosed and treated while only 5 to 6 mm. in diameter. In the earlier stages both adenocarcinomas and mixed tumors of the palate appear as nonulcerated, nontender, sharply delimited rounded or ovoid submucous masses which produce a smooth bulge from the mucous surface and resemble such benign lesions as retention cysts. The mucosa overlying the small or moderate-sized lesions always appears normal.

From the standpoint of morbid anatomy, adenoid tumors possess a smooth contour and a sharply delimited border and in most cases have a definite capsule, at least until they have reached a diameter of 2 to 3 cm. The more malignant adenocarcinomas, however, tend to exhibit invasive tendencies more often than benign mixed tumors.

In the hard palate adenoid tumors, even adenocarcinomas, do not ordinarily produce perforation of the bone early in the course of the disease. When perforation occurs, it appears to be due more to erosion by pressure than to actual invasion of the bone as in epidermoid carcinoma. As the ovoid tumor enlarges in the soft palate, it tends to form a diffuse bulge on the lower surface, which may also extend to the upper.

Adenoid tumors, even though large, rarely produce ulceration of the mucous membrane. In the present series an adenocarcinoma ulcerated to the mucous membrane in only 1 of 16 cases, and in that instance the ulceration may have been due to the implantation of radon seeds at another clinic before the patient's admission to the Memorial Hospital. Ulceration was observed in 2 cases of benign mixed tumor; in one the growth had been present for twenty-five years; in the other the ulceration was due to a recurrence of the growth in the operative scar after incomplete removal at another hospital.

The growth of adenocarcinoma appears to be more rapid (average duration in the present series three years) than that of mixed tumor (average duration over five years), but both varieties may be of exceptionally long duration. In the present series 1 mixed tumor, 5 cm. in diameter, had been present for about twenty-five years, and 1 adenocarcinoma, 7 cm. in diameter, had been present for fifteen years. It is possible that the long duration of the latter was due to the fact that a benign mixed tumor had undergone more recent malignant degeneration. The shortest alleged duration was one week in the case of a mixed tumor, but since the lesion was 2 cm. in diameter it had obviously been present over a much longer period. New and Childrey [4] reported an average duration of about four and a half years for adenocarcinoma and Ahlbom [5] a duration of about six years for all mucous and salivary gland

tumors. The latter made the definite statement that there is little difference in duration of symptoms between the malignant and benign types; this does not agree with observations of palatal salivary gland tumors at the Memorial Hospital.

In brief, the most important clinical characteristics of adenoid tumors of the palate, both mixed tumors and adenocarcinomas, are, first, a slow rate of growth and, second, a noninfiltrative, encapsulated character. The growth of adenocarcinoma tends to follow a benign course for a long time, the local lesion resembling a benign mixed tumor and causing few if any symptoms. If the tumor is left uncontrolled, death seldom results from complications of the primary lesion but almost always is due to generalized metastasis. The shortest duration of life in any of the cases of unsuccessfully treated adenocarcinoma in this series was one year; death occurred as the result of complications of treatment. Excluding this case, the average duration of life in the fatal cases was about six and a half years.

The average duration of life from the onset of symptoms in the fatal cases of epidermoid carcinoma was one and a half years; in fatal cases of adenocarcinoma it was five years. There should be little difficulty in the local control of either malignant or benign mucous and salivary gland tumors of the palate. The small or even the fairly large tumors are sufficiently delimited and accessible in the palate to permit complete surgical removal, and it is only when these growths have deeply infiltrated the lateral pharyngeal walls or extended onto the base of the tongue that they become inoperable. Abshier [3] and Goldsmith and Ireland [12] mentioned the tendency of mixed tumors in the palate to recur locally, which seems to me to indicate an unnecessarily incomplete removal. Rhoads and Mecray,[7] on the other hand, stated that recurrences of mixed tumors are extremely rare. In the palate the mucous and salivary gland tumors are almost invariably single, and recurrences can be due only to incomplete removal. In the parotid gland, although recurrences should still be rare, the possibility is greater, even after surgical removal, for it is well known that mixed tumors may be multiple and that adenocarcinomas tend to infiltrate the gland substance at an earlier stage. In Ahlbom's report, so far as I can determine, there is no definite statement as to the number of recurrences following surgical removal of salivary gland tumors of the palate.

Metastases.—In the present series metastases were demonstrated clinically in 45 per cent of the patients with malignant tumors on admission and developed later in an additional 16 per cent, so that in 61 per cent metastases were present at some time during the course of the

12. Goldsmith, P. G., and Ireland, P. E.: Mixed Tumors in the Nose and Throat, Ann. Otol., Rhin. & Laryng. **45**:940, 1936.

disease. This figure is about the same as that for patients with cancer of the tongue and of the cheek, but it is less than that for patients with cancer of the nasopharynx and of the tonsil. If the lesions are separated into those which arise definitely in the hard and those which arise in the soft palate, excluding those at the junction of the two palates, it is apparent from the present series that malignant growths of the soft palate are much more likely to metastasize (72 per cent) than those of the hard palate (42 per cent). The comparatively high incidence of metastases from tumors of the soft palate may probably be accounted for by the mobility of this structure, which favors the detachment of tumor emboli. The converse is true of the fixed hard palate.

In the present series, epidermoid carcinoma appeared much more likely to metastasize (69 per cent of the cases) than adenocarcinoma (27 per cent), but a preponderance of metastases from the soft palate was common to both histologic forms of growth. New and Childrey [4] made the rather ambiguous statement that about 16 per cent of the patients with adenocarcinoma of the palate had "enlarged cervical nodes", but they gave no information as to any subsequent clinical or histologic confirmation in their cases.

The lymph nodes most frequently involved first were the subdigastric (upper deep cervical) nodes of the internal juglar chain (in 72 per cent of the cases with metastases). The lymph nodes involved next in order of frequency were the prevascular or retrovascular nodes of the submaxillary group (16 per cent). After involvement of these nodes, the disease progressed in order to the middle and inferior nodes of the internal juglar chain. It is well known that adenocarcinoma of the oral cavity or of the skin of the head and neck may metastasize systemically without involvement of the intervening lymph nodes. In Watson's series of patients with intraoral adenocarcinoma from the Memorial Hospital, 10 had systemic metastases and only 5 (50 per cent) of these had metastases to the cervical lymph nodes. Of patients with palatal adenocarcinoma in the present series, 2 had systemic metastases but neither had involvement of the cervical lymph nodes.

Systemic Metastases.—In the autopsy records [13] of the Memorial Hospital there are 8 cases of patients who died of epidermoid carcinoma of the palate, and in 1 of these there were systemic metastases to the following sites: liver, peritoneum, bladder, adrenals, myocardium, skeletal system, skeletal muscles, lungs, skin and choroid plexus. There are also 3 cases of patients who died of adenocarcinoma of the palate, and in 2 of these there were systemic metastases.

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13. Braund, R. R., and Martin, H. E.: Distant Metastases in Cancer of the Upper Respiratory and Alimentary Tracts, Surg., Gynec. & Obst. **73**:63, 1941.

HISTOPATHOLOGY

The histologic distribution of the palatal neoplasms in the present series is given in table 2. Benign tumors (of salivary gland origin) comprise about 7 per cent of the series and malignant tumors (epidermoid and adenocarcinoma) about 93 per cent. Of the malignant tumors, epidermoid carcinoma makes up about 83 per cent and adenocarcinoma about 17 per cent. There were in addition 1 melanoma and 1 rhabdomyosarcoma. Lymphosarcoma occasionally arises in the palate, although there was none in this location in the present series. Benign leiomyosarcoma has been reported as occurring in this area, but none so situated is on record at the Memorial Hospital.

From the histologic standpoint epidermoid carcinoma of the palate does not differ materially from epidermoid carcinoma of other regions of the oral mucous membranes; hence this subject requires no detailed

TABLE 2.—*Histologic Distribution of Palatal Tumors Observed at Memorial Hospital*

I. Epidermoid tumors		74
Squamous cell	67	
Transitional cell	6	
Melanoma	1	
II. Glandular tumors		24
Adenocarcinoma	16	
Mixed tumors of salivary gland type	8	
III. Mesodermal tumors		1
Rhabdomyosarcoma	1	
Total		99 *

* In the remaining 2 cases the patients were referred for treatment of metastases; there was no disease in the primary site.

analysis in this report. In the present series there were 6 transitional cell carcinomas, 3 in the soft palate and 3 in the hard.

Adenoid tumors (adenocarcinomas and benign mixed tumors) comprise about 23 per cent of all palatal tumors. These glandular tumors of the palate are presumably derived from minor salivary and mucous glands of the oral mucosa and show every variety of structure seen in the major salivary glands. Tumors resembling those arising in minor salivary glands are occasionally encountered beyond the limits of the oral cavity—in the esophagus, in the subglottic region, in the lower part of the trachea, in the primary bronchi, where they presumably arise from mucous glands, and in the nasal cavity. The sweat glands occasionally produce tumors indistinguishable from salivary gland mixed tumors. So also, rarely, does the breast, especially in dogs. In all of these areas tumors varying in structure from adenocarcinoma to a relatively benign mixed cystic structure may arise.

The theories held by some that these adenoid tumors arise from embryonic rests, from misplaced remnants of the salivary glands or from

branchial pouches are, it seems to me, superfluous. In the first place, these tumors occur frequently outside the areas of the branchial pouches. In the second place, the normal mucosa, where these tumors arise, contains glandular structures (racemose and mucous), and the relative incidence of these tumors in various sites corresponds closely to the relative abundance of minor salivary glands in the mucosa. For example, their incidence in the palate, the base of the tongue and the tonsillar pillars, structures which contain a relatively large number of minor salivary and mucous glands, is much greater than their incidence in the lip, the anterior portion of the tongue, the mucosa of the cheek and the nasopharynx, where there are relatively few of these glands. In the nasal cavity, where the mucous glands are numerous, a bizarre variety of neoplasms arise, a large proportion of which have adenoid elements, although they do not follow closely the characteristics of palatal adenoid tumors.

The literature on the classification of salivary and mucous gland tumors, both of the major and of the minor salivary glands, is extremely complex and confusing, especially since there is a tendency to combine morphologic and embryologic distinctions in the same classification. Ahlbom,[5] after reviewing the literature and rejecting most of the newer concepts, returned to the more simple classification of Masson and Peyron [14]; that is, he separated these tumors into benign mixed tumors, semimalignant mixed tumors and malignant tumors (adenocarcinoma). It is my opinion that any attempt at a clear classification of these growths is artificial, since there is probably a gradual transition from the definitely benign mixed tumors through the increasing degree of cellularity of the intermediate grades to the other extreme of highly malignant adenocarcinomas. The designation by some authors of a semimalignant group is obviously either a frank or an unwitting admission of this gradual transition or intermediate stage in which the exact diagnosis is uncertain. Finally, as opposed to a clear classification into definite groups, it can be stated with certainty that the histologic and clinical character does not remain fixed within an individual tumor and that a growth which begins as a benign mixed tumor may, after a varying period, undergo malignant degeneration, so that eventually the clinical course may progress to a rapid termination with a widely metastasizing adenocarcinoma.[15]

14. Masson and Peyron: A propos des tumeurs mixtes des glandes salivaires. Spécificité cellulaire et tumeurs mixtes, Bull. Assoc. franç. p. l'étude du cancer **7**:219, 1914.

15. An example of malignant degeneration of a benign mixed tumor is found in the following case: A doctor first noted a subcutaneous tumor in his parotid region about 1910. The growth was excised after having been diagnosed as a benign mixed tumor; the diagnosis was proved to be correct on histologic exami-

Dr. Fred Stewart, pathologist at the Memorial Hospital, has reviewed the histologic material included in this report and makes the following comments on the histogenesis of mucous and minor salivary gland tumors:

The "mixed" tumors reveal a complex histologic structure, consisting of epithelial elements in the form of strands, masses, tubules or alveoli, together with mucoid pseudomesoblastic tissue and cartilage. Any of these elements may predominate to produce the appearance of a pure structure, such, for example, as chondroma or myxoma. Most pathologists now accept the purely epithelial origin of the cells and regard the mucoid tissue, spindle cell areas and cartilage as metaplastic in nature; hence they employ the term "mixed tumor" to describe structure rather than to imply complex origin. The purely epithelial origin of these lesions was clearly recognized by Krompecher [16] and has gained wide credence.

The frankly carcinomatous tumors of minor salivary glands are of several types and presumably of several origins, although the average tumor when first seen is too advanced to enable one to decide its exact origin definitely. Carcinomas are more or less divisible according to distinct morphologic patterns but frequently reveal transition pictures making it difficult to place them in single categories. Thus, in a "mixed" tumor differences in size and shape of cells, nuclear variability and hyperchromatism enable one to predict or suspect an eventual recurring malignant clinical course. The lesion recurs and metastasizes as alveolar carcinoma, rarely as a malignant "mixed" tumor of complex structure.

Certain tumors which pursue a malignant course are best designated as cylindromas from their resemblance to basal cell tumors of the skin. Others resemble the common adenoid basal cell tumors of the skin and show solid cords of epithelial cells interrupted by glandlike spaces or small cysts. These have been designated as adenoid cystic adenocarcinomas. When they arise in a mucous membrane derivative they are uniformly malignant and may metastasize as widely as any known type of tumor—to nodes, serous membranes, thoracic and abdominal (and even pelvic) viscera and bones. Occasionally the mucoid pseudomesoblastic element of a mixed tumor yields metastases which resemble the structure of pure myxosarcoma. Mixed tumors or pure carcinomas may exhibit epidermoid or squamous areas, either as a form of metaplasia or because a duct element is present. Thus the picture of squamous carcinoma arises. Pure solid or small alveolar carcinomas are rarely encountered; they run a malignant course.

Rarely in the oral cavity one finds pure mucous gland cancer of papillary or alveolar structure resembling cancer of the stomach or of the lower gastrointestinal

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nation. The growth recurred after a few years. About eight or nine years later it was again excised and again found to be a benign mixed tumor. About 1925 there was a further recurrence, followed by a third excision, but at that time the growth histologically was adenocarcinoma. A fourth recurrence took place, and the patient was seen at the Memorial Hospital with a typical deeply invading postoperative adenocarcinoma of the parotid gland. He finally died of local recurrence and disseminated cancer. The slides of the earlier operation were all reviewed by Dr. Fred Stewart at the Memorial Hospital, who found the tissue removed at the first two operations to be clearly representative of benign mixed tumor, whereas the later specimens were representative of adenocarcinoma.

16. Krompecher, E.: Zur Histogenese und Morphologie der Mischgeschwülste der Haut sowie der Speichel- und Schleimdrüsen, Beitr. z. path. Anat. u. z. allg. Path. **44**:51, 1908.

tract and indistinguishable microscopically from such tumors. A peculiar clear cell cancer of minor salivary gland origin or of mucous gland origin may be indistinguishable from metastatic renal clear cell cancer.

The only absolute criterion of malignancy of salivary or mucous gland tumors is their capacity to metastasize. Eggers [17] and others have perhaps overemphasized perforation of the capsule as a malignant characteristic of these tumors. While it is conceded that perforation of the capsule and local infiltration are often a characteristic of tumors which metastasize, it must be admitted that such local invasion without metastasis does not by itself render a given tumor malignant. Even the most malignant metastasizing salivary and mucous gland tumors may remain encapsulated but nevertheless metastasize widely. Furthermore, postoperative recurrences of benign mixed tumors may infiltrate the local tissues.

Melanoma, which occurs more commonly on the gums than in any other part of the oral cavity, occurs next in frequency on adjacent structures, namely, the hard palate and the mucosa of the cheeks. In the present series there was 1 case of melanoma, in a man 65 years of age, who died, after two years of generalized metastases. There was also 1 case of rhabdomyosarcoma, in a child of 8 years. The growth was moderately radiosensitive but recurred locally and finally metastasized to the lungs; the patient died after fifteen months. There was another case of rhabdomyosarcoma, more recent than the present series. The tumor originated in the soft palate; it recurred repeatedly after removal by cautery, but was finally controlled locally. At the time of writing the patient has survived without recurrence for two years since the last treatment.

DIAGNOSIS

Several varieties of benign lesions and tumors occur in the palate and may at times present problems in differential diagnosis. The benign nature of some of these lesions, such as torus palatinus and dentigerous cyst, should be immediately apparent on clinical examination alone. With others, especially when there is ulceration, a confirmation of the diagnosis should be made by biopsy prior to the institution of the necessarily aggressive treatment for cancer, either surgical or radiologic. In the case of a superficially ulcerated lesion a specimen for biopsy is readily removed. In the case of a nonulcerated submucous tumor, incision through intact mucous membrane for the removal of a specimen is highly objectionable, since the maintenance of an intact capsule is of paramount importance in the complete surgical removal. I do not believe that surgical biopsy can be the direct cause of malignant

17. Eggers, H. E.: Mixed Tumors of the Palate, Arch. Path. **6**:378 (Sept.) 1928.

transformation of a benign mixed tumor. The risk of permitting a tumor to spill outside its capsule, thus making its subsequent removal more difficult or increasing the chance of metastasis, is sufficient argument against surgical biopsy of these tumors.

In cases of these nonulcerated tumors aspiration biopsy finds one of its most definite indications. From the aspirated specimen it is not always possible to differentiate between benign mixed tumor and adenocarcinoma, but this point is of only minor importance since the treatment, surgical removal, is the same in either case and the exact histologic classification can safely await the microscopic examination of excised tumor.

Cancer of the antrum may invade the bony antral floor, and the growth, under pressure in the antral cavity, may then produce a bulge of the palate without perforating the mucous membrane. This bulge may be mistaken for an adenoid tumor of the palate. The differential diagnosis can ordinarily be made by roentgenographic examination, which demonstrates an opacity of the antral cavity and destruction of its other bony walls. Such an antral growth is also likely to be found invading the nasal cavity. The diagnosis may be confirmed by aspiration biopsy of the antral cavity either through the palate or through the cheek. If epidermoid carcinoma is found on aspiration biopsy of a nonulcerated bulging tumor of the hard palate, the diagnosis of antral rather than palatal cancer is almost certain.

Delay in Diagnosis.—As might be expected, diagnosis of the slowly growing adenoid tumors is delayed longer (thirty-five months from the beginning of symptoms) than that of the epidermoid growths (seven months). When medical advice is first sought, the diagnosis is missed in about 25 per cent of the cases of both the adenoid and the epidermoid tumors, and the patients are given some form of local treatment, such as mouth washes or topical applications, or they are assured that the lesion is of no particular significance. As in most cases in which the physician or the dentist fails to recognize cancer when he first sees it, the fault arises both because of unfamiliarity with the appearance of cancer and because of failure to recognize the importance to the patient of immediate diagnosis and treatment.

Differential Diagnosis.—Benign lesions which may be confused with neoplasms of the palate will be discussed separately.

(*a*) Granuloma or Simple Ulcer: During the period covered by the present report, 17 patients with granuloma or nonspecific ulcer applied or were referred for a differential diagnosis of cancer—about one sixth as many as the whole group of patients with cancer. Such benign lesions are not uncommonly observed in the midline of the hard palate in heavy smokers, and they cannot be differentiated clinically from cancer. The correct diagnosis is made by biopsy.

(*b*) Papilloma: As in all parts of the oral mucous membrane, in the palate the neoplastic response to chronic irritation may take the form of papilloma rather than of carcinoma. In the hard palate such a lesion usually occurs near the midline and may in rare instances spread over considerable areas of the palate. In the soft palate it occurs as papillary warty projections, which the experienced observer can diagnose clinically. Eleven patients with papilloma were admitted to the hospital during the period of the present report (one tenth as many as the patients with carcinoma). The treatment is preferably by strictly local removal with the actual cautery. Radiation therapy should not be used for these benign epithelial growths of the palate.

(*c*) Torus Palatinus: This lesion is an osteoma which occurs at about the center of the hard palate where the two maxillas are fused in the midline. If careful examinations are made, a slight prominence at this point is found in a high percentage of otherwise normal adults. In some persons the lesion takes on greater growth and forms a hard, fixed, smooth or nodular prominence, 2 to 4 cm. in diameter, covered by normal mucous membrane. Its true character—that is, solid bone overlaid by normal mucous membrane—is fairly obvious on close examination. The lesion has no significance except that in some instances it interferes with the proper fit of a dental plate. If so desired, the bony tumor may be removed by a chisel and the base left to heal by granulation and epithelization from the borders. Seven patients with torus palatinus applied to the Memorial Hospital during the period covered by the present report.

(*d*) Syphilis: Gumma of the oral mucous membrane cannot be distinguished clinically from cancer, but it is extremely rare. No gumma of the palate was encountered during the period covered by the present report, although since this series was collected 2 such lesions have been observed, both proved to be gumma by biopsy, which was negative for cancer, positive Wassermann tests and a therapeutic test (that is, they disappeared under antisyphilitic treatment).

(*e*) Dentigerous Cyst or Adamantinoma: Either a benign dentigerous cyst or an adamantinoma of the upper jaw may produce a smooth rounded cyst of the palate which can be mistaken for an adenoid tumor. The diagnosis should be made by roentgenographic studies and aspiration biopsy. A correct diagnosis is important from the standpoint of treatment. A dentigerous cyst should be opened widely and drained, and the cyst wall left as the epithelial covering of part of the defect. Adamantinoma of the upper jaw always originates within the bony structure, and although it occasionally produces a bulge on the hard palate, it will be found on closer examination to have an even wider extent in the other portions of the maxilla. The surgical removal of an

adamantinoma necessitates much wider excision of bone than the removal of an adenoid tumor or of a dentigerous cyst arising in the hard palate.

TREATMENT OF THE PRIMARY LESION IN CANCER OF THE PALATE

The selection of the method of treatment of a palatal tumor depends both on the histologic variety and the site of the tumor (hard or soft palate). In general the adenoid growths, both mixed tumors and adenocarcinomas, are radioresistant. There seems to be little difference between the two, although adenocarcinoma may occasionally be moderately more radiosensitive. To be cancer lethal, the dose of radiation for these adenoid tumors must be large enough to produce radionecrosis in almost all cases. Even then it may still fail to sterilize all parts of the tumor, and the chance of local recurrence is high. In contradistinction to the superficial eroding indefinitely outlined epidermoid carcinomas of mucous membrane, these submucosal adenoid growths tend to be globular or ovoid with sharply delimited borders and sometimes with a definite capsule. The latter characteristics of adenoid tumors coupled with their high radioresistance makes them more suitable to surgical removal than to radiation treatment.

Mild preoperative or postoperative irradiation of these radioresistant tumors is illogical. Most authors have favored surgical excision rather than irradiation of these adenoid tumors, but with the exception of Abshier [3] they have recommended either preoperative or postoperative irradiation. Ahlbom [5] expressed the belief that treatment should always begin with fractionated external irradiation except for the clearly benign mixed tumors. After irradiation he recommended electrosurgery and then postoperative irradiation. Some authors [13] have recommended postoperative irradiation in all cases, usually by placing radium in the wound cavity.

It seems to me that such preoperative and postoperative irradiation of these highly radioresistant, operable benign and malignant salivary gland tumors of the palate is illogical. If, as is possible in most cases, the tumor has been completely removed, irradiation can be of no benefit and only retards healing. If a portion of the tumor has been left, the application of sublethal doses of radiation can be of no benefit, and cancer-lethal irradiation of recurrent nodules must be so aggressive as to be unsafe except in a very limited volume of tissue. In my opinion mild preoperative and postoperative irradiation of cancer is an arbitrary

18. Bland-Sutton, J.: Tumours, Innocent and Malignant, ed. 7, London, Cassell & Co., 1922, p. 414. Hill, F. T.: Mixed Tumors of the Hard Palate, Ann. Otol., Rhin. & Laryng. **47**:317, 1938. Seltz, S.: A Case of Adenosarcoma of the Palate, J. Med. **17**:87, 1936. Ahlbom.[5] Goldsmith and Ireland.[12]

custom which has persisted in many clinics from the days when the action of radiation on malignant tumors was not well understood and when it was believed that mild irradiation of cancer was always of benefit to the patient even though it produced no visible effect on the growth. The application of mild doses of radiation over large volumes of tissue is not without its harmful constitutional effects.

Epidermoid carcinoma of the palate exhibits about the same radiosensitivity as other epidermoid growths of the oral cavity. These epidermoid tumors in the soft palate tend to be highly radiosensitive, as are the adjacent pharyngeal growths (in the tonsil, base of tongue, extrinsic larynx, etc.). In the soft palate particularly, epidermoid carcinomas infiltrate early and irregularly, making wide surgical removal difficult in a structure which is functionally important and where defects are almost impossible to repair surgically or even mechanically by prosthetic appliances. The chance of curing epidermoid carcinoma of the soft palate is much greater by irradiation than surgical removal.

In the hard palate an epidermoid carcinoma arising in the thin layer (2 to 3 mm.) of soft tissues overlying bone is in immediate contact with bone, or at least with periosteum, in all cases. Application of cancer-lethal doses of irradiation to such a growth always considerably devitalizes the underlying bone and often results in the exposure of the heavily irradiated bone, with inevitable radio-osteomyelitis and a long period of morbidity, until sequestration has taken place. For this reason, surgical removal of epidermoid carcinoma of the hard palate by cautery and chisel is often preferable to radiation therapy.

In brief, the treatment of adenocarcinoma and of mixed tumors of the hard or the soft palate is preferably by surgical removal. Epidermoid carcinoma of the hard palate is usually best treated by surgical removal, though occasionally radiation therapy or combinations of radiation therapy and surgical removal are indicated. For epidermoid carcinoma of the soft palate radiation therapy is almost always the method of choice.

The technics of treatment for the various areas of the palate will be described under separate headings and in the legends which accompany the illustrations.

Surgical Removal of Palatal Tumors.—The most efficient instrument for the surgical excision of palatal tumors is the actual cautery, with the assistance of a chisel for the removal of underlying bone in the hard palate. For a tumor of the hard palate, a moderate-sized, red-hot cautery loop should be used to cut through the soft tissues down to the bone, the line of excision including a safely wide margin (5 to 10 mm.) of normal tissue at the border of the growth (fig. 2*A*). After preliminary incision of the overlying soft parts by cautery, the underlying bone is cut through with a bone chisel, the lesion removed, and the projecting spicules of bone smoothed down with a rongeur (fig.

2 *B* and *C*). Such a procedure always includes opening and removal of the floor of the antral cavity or of the nasal cavity or of both. The wound should be packed immediately to prevent hemorrhage. Bone wax may be used to plug larger spurting vessels emerging from the bone. In some instances of mixed tumor or adenocarcinoma of the hard palate, it may be safe to strip the capsule and the periosteum from the bone without making a perforation (figs. 3 and 4). The judgment of the surgeon must determine whether or not such a conservative plan is justified from the standpoint of safety in the individual case. In the

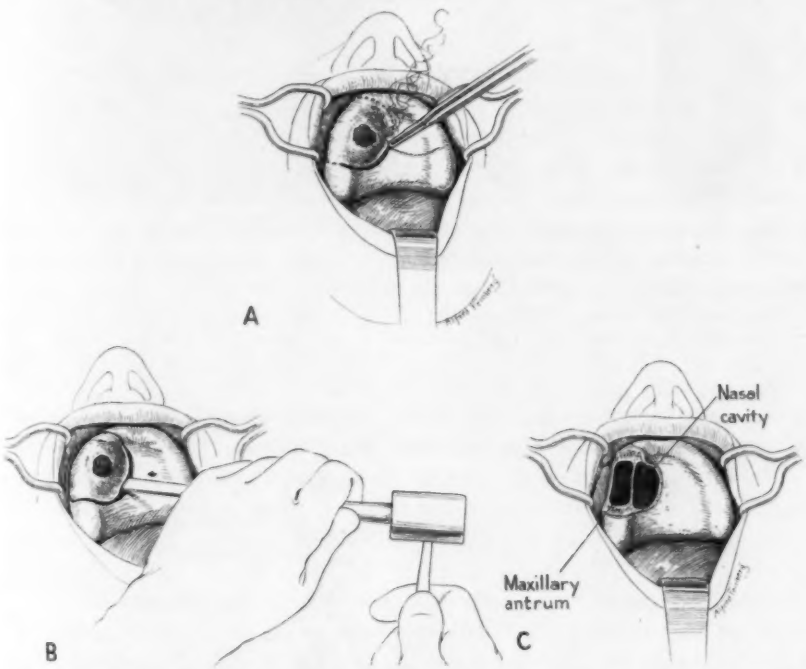

Fig. 2.—Surgical excision of a palatal tumor by cautery and chisel. *A*, the growth is circumscribed by cutting through the soft tissues overlying the palate and the alveolar process with a fine-bladed actual cautery. *B*, with a sharp chisel and a mallet the bone underlying the tumor is mobilized. *C*, the tumor with the underlying bone is removed, exposing the maxillary antrum and the nasal cavity.

case of epidermoid carcinoma of the hard palate, underlying bone should always be removed.

In the soft palate only the adenoid tumors should be treated by cautery removal, and an effort should be made in all cases to avoid through and through perforation of the structure if at all possible. A finer caliber cautery loop should be employed in the soft palate than in the hard. An area of the overlying mucous membrane should be

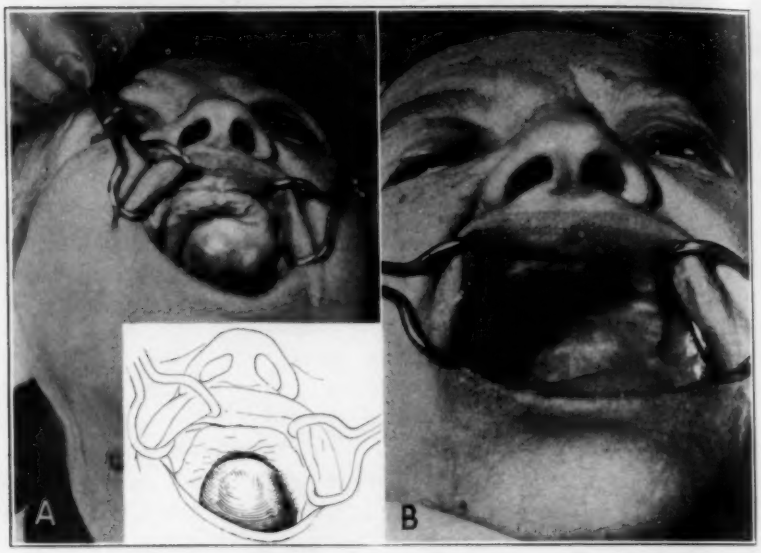

Fig. 3.—M. G., a woman aged 67, was admitted to the hospital April 17, 1936, with a swelling of the palate of fifteen years' duration. There was a bulging, ulcerated, slightly fluctuant tumor covering almost the entire hard palate (*A*). The insert shows the extent of the tumor. Physical examination and roentgenographic study indicated that the bone of the palate had not been invaded by the growth. The tumor was excised by cautery and periosteal elevator without removal of any bone. Histologic examination showed a mixed tumor of the salivary gland type. Healing took place by secondary intention, and there has been no recurrence in the palate after five years (*B*).

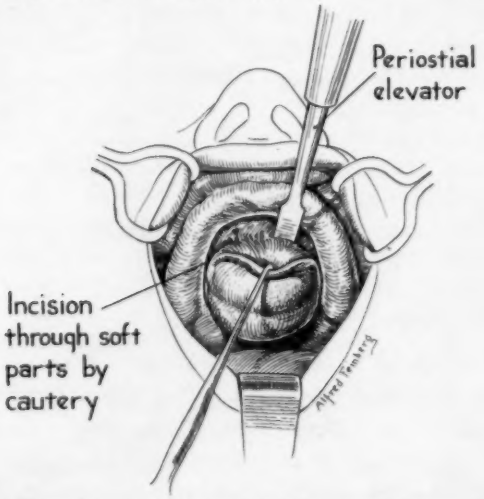

Fig. 4.—Surgical excision of relatively benign cystic tumor of the palate which does not invade bone. The tumor is circumscribed by an incision with the actual cautery as shown in figure 2 *A*. The growth is then mobilized from the hard palate by blunt dissection with a periosteal elevator.

removed with the tumor. A useful point in the technic is the placement of one or two silk or dermal sutures in the mucous membrane and the capsule near the center of the tumor to produce immobilization and some traction on the growth which would otherwise tend to be depressed into the palate, so as to obscure the intended line of incision. By working slowly, guided by digital palpation, an extracapsular dissection by the cautery is carried out, and by clamping and tying a few moderately sized blood vessels the procedure in many instances can be kept practically bloodless. The wound is left open to heal by granulation except in the case of a small tumor, in which one or two sutures may be used to close the incision loosely.

In the expansile growth of the larger adenoid tumors of the soft palate, especially those which arise near the free border, there may be deep fixation in the tonsillar region; in the treatment of such a tumor the cautery can be used only at the beginning of the operation. When the apex of the tumor has been freed, the rest of the operation must be carried out mainly by blunt dissection and by enucleation with the fingers. When such a larger tumor is situated laterally, the operation had best be preceded by ligation of the external carotid artery on the involved side. There is a consistent tendency of all adenoid tumors of the palate and of the tonsillar region to remain sharply delimited and noninfiltrating, so that even for the larger growths (5 to 6 cm. in diameter) the possibility of complete removal by enucleation should always be considered. Unless the surgeon is fully conversant with the morbid anatomy of these adenoid tumors, he is likely to overlook the fair possibility of permanent control by surgical removal and to consign the patients at once to radiation therapy, which offers little or nothing, even from the standpoint of palliation, with these bulky, radioresistant growths.

In the present series, 2 adenocarcinomas were treated by surgical excision alone (fig. 5), 2 by a combination of irradiation and surgical removal (fig. 6) and 2 by irradiation alone. Of the 4 successfully treated epidermoid carcinomas of the hard palate, 2 were treated by a combination of irradiation and surgical removal and 2 by surgical removal alone.

Combinations of Irradiation and Surgical Removal in the Treatment of Palatal Tumors.—Surgical removal of a residual or a recurrent palatal tumor after radiation therapy is sometimes indicated, or it may be of advantage to remove an area of devitalized or radionecrotic soft tissue and bone after complete destruction of the growth by irradiation.

Formerly at the Memorial Hospital many adenocarcinomas were treated by heavy interstitial irradiation and cautery removal after a week to ten days. The rationale of such a procedure was that there would be a cancer-lethal radiation effect at the line of excision, so that

the chance of recurrence would be much reduced. In view of the high radioresistance of these adenoid tumors as well as of their sharp delimitation it is probable that such a combination of irradiation and surgical treatment is not superior to surgical removal alone. Although in our series such combinations were successful in several instances, it is significant that there were no recurrences following simple surgical removal even when the irradiation was omitted.

Radiation Treatment of Palatal Tumors.—As has been mentioned previously, irradiation should not be used for adenoid tumors of the palate if there is a chance of their surgical removal. In the hard palate

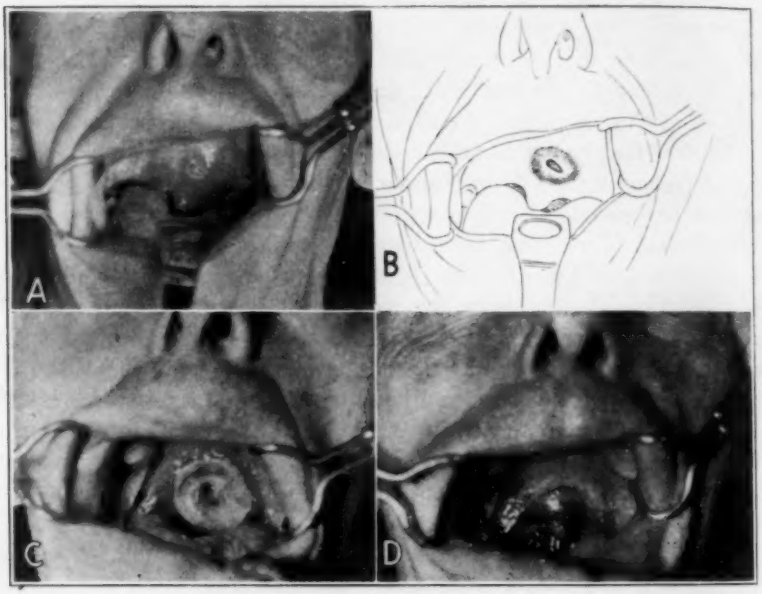

Fig. 5.—G. B., a man aged 61, was admitted to the hospital Dec. 8, 1936, with a diagnosis of adenocarcinoma of the palate. The primary lesion in the left soft palate crossed the midline (*A* and *B*). The growth, 2 cm. in diameter, originally nonulcerated, had been incised for biopsy before admission. The lesion was removed by the fine loop of an actual cautery with the region under local anesthesia (*C*). Healing took place by secondary intention, and the growth has not recurred (*D*). After an irregular follow-up, bilateral cervical metastases were discovered two and a half years later. Bilateral neck dissection was performed in two stages with an interval of two months between the operations, the internal jugular vein being removed only on the left side. Histologic examination showed metastatic invasion of lymph nodes on both sides. After these neck dissections the patient has remained well for two years.

even epidermoid carcinomas are not always best suited to radiation therapy. The selection of the exact method of treatment is often optional and may depend on the facilities available and on the experience and

ability of the individual surgeon with the various methods. If irradiation is used for a tumor in the hard palate, the technic is similar to that for a tumor in the soft palate, which is as follows:

In irradiating palatal tumors an attempt should be made to rely mainly on roentgen radiation given perorally, so as to spare the soft tissues of the cheeks and the parotid salivary glands. If a palatal growth is so large or extends so far down the lateral pharyngeal wall that the largest preoral portal does not include all of the lesion, additional treatment must be given through the skin of the cheeks. The smaller or

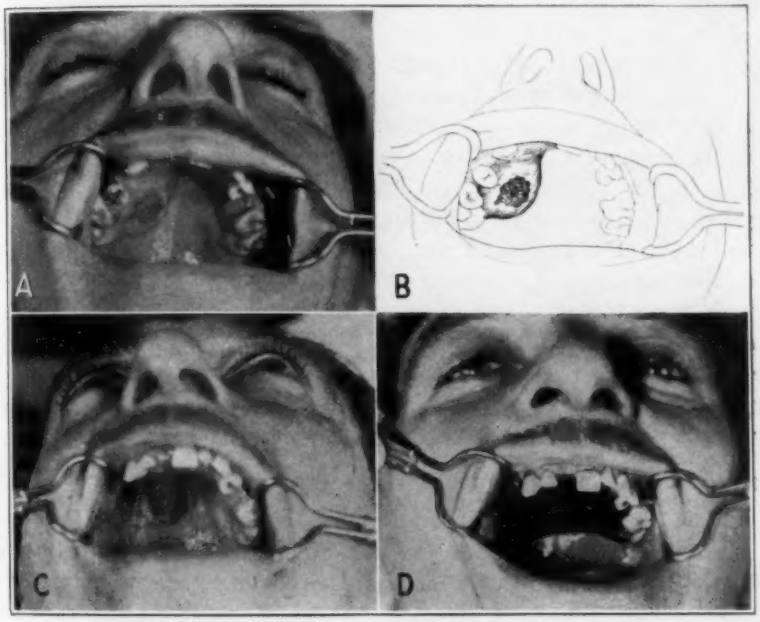

Fig. 6.—C. A., a man aged 28, was admitted to the hospital Sept. 11, 1936, with a history of a swelling in the right side of the hard palate of four years' duration. Examination revealed a diffuse firm swelling of the right side of the hard palate 3 cm. in diameter with an area of ulceration 1.5 cm. in diameter (*A* and *B*). Histologic examination showed a mixed tumor of salivary gland type which was becoming carcinomatous. The lesion appeared to be definitely attached to the bone, if not invading it. The growth was treated by radon gold seeds (21 millicuries) followed in one week by wide excision with chisel and cautery. Healing took place with a large defect in the right side of the hard palate (*C*). The defect was closed by a prosthesis which completely restored normal speech and relieved disability in swallowing. The patient has remained well for five years (*D*).

average-sized palatal growths (up to 3 to 4 cm. in diameter) can be approached perorally, using cylinders between 3.5 and 4.5 cm. in diameter, accurately centered with a lighted periscope, as described in

previous publications.[19] A daily dose of 300 to 400 r is given for a total of 7,000 to 8,000 r with high voltage (200 to 250 kilovolts) radiation or 12,000 to 14,000 r if low voltage (100 to 120 kilovolts) should be used. When the growths are on the surface, the shortest practical target-skin distance (15 to 25 cm.) should be employed. If external portals are used in addition to the peroral, these should be directed through the skin of the cheeks, the exact centering being carefully determined and marked on the skin, preferably by a small tattoo mark.[20] The external portals may be 6 to 7 cm. in diameter. With the use of such multiple portals, the individual and total doses are variable and empiric.

After the external irradiation, depending on the response of the lesion, it is usually of advantage to apply a supplementary dose of radon seeds interstitially. In most cases such supplementary interstitial irradiation is preferable to an attempt to control the disease entirely by external irradiation. The dose of seeds is somewhat empiric and varies widely in the individual case. The individual strength of the radon seeds should be about 1.5 millicuries. For growths of the hard palate, dependence must be placed mainly on external (peroral) irradiation, since the thin layer of soft tissue overlying the bone is usually not great enough to permit retention of interstitial implants. This is one of the reasons why external irradiation is not so successful in the hard as in the soft palate. The largest successful dose of radon seeds used in combination with external irradiation in the treatment of epidermoid carcinoma of the soft palate in the present series was 20 millicuries.

TREATMENT OF CERVICAL METASTASES FROM CANCER OF THE PALATE

In the Head and Neck Clinic at the Memorial Hospital the treatment of cervical metastases from epidermoid carcinoma of the palate does not differ from that of metastases from other forms of intraoral cancer.[21] If no metastases are clinically demonstrable on admission, no

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19. (*a*) Martin, H. E., and Sugarbaker, E. D.: Cancer of the Tonsil, Am. J. Surg. **52**:158, 1941. (*b*) Martin, H. E.: Variations in Radiation Technic and Biologic Effects in the Treatment of Pharyngeal Cancer, Radiology **34**:149, 1940.

20. The skin is cleansed with alcohol, and a small drop of india ink is placed at the selected point. With a sterile sharp-pointed surgical needle, several punctures are made through the india ink into the skin. Such a mark remains permanently, but its size can be so small as to be unobjectionable.

21. Few authors have mentioned the treatment of cervical metastases from palatal tumors except Ahlbom,[8] who in a discussion of all mucous and salivary gland tumors recommended prophylactic irradiation of the cervical lymph nodes in all cases of malignant salivary gland tumor. It is difficult to see the logic of such a procedure, especially for these radioresistant tumors, as the radiation control of even the localized primary lesion can hardly be accomplished without producing radionecrosis. Ahlbom agreed with the policy of the Memorial Hospital of per-

treatment of any kind is given to the neck. If the primary lesion is controlled, the patient is kept under systematic observation, both for recurrence in the primary site and for metastasis to the neck, and treatment to the neck is given only if and when metastases develop. The soundness of such a policy of watchful waiting is based on the analysis of the clinical behavior of metastases from intraoral cancer in general and has been discussed repeatedly in previous reports from this clinic.

If there is palpable involvement of the cervical lymph nodes by epidermoid carcinoma on admission, the treatment in most cases should be by irradiation—fractionated roentgen radiation through small portals to the individual nodes, supplemented by implantation of radon seeds. The indication for radiologic rather than surgical treatment in these cases is that if metastases are present on admission the growth in the palate is almost invariably far advanced and suitable only to treatment by aggressive irradiation. Neck dissection in these cases cannot be performed in conjunction with the aggressive irradiation of the palatal growth and is therefore of little or no value in the treatment of metastatic nodes already present on admission.

The detailed technic of radiation therapy for metastatic cervical cancer has been described previously [22] and will not be repeated here except in brief outline. The dosage is variable and depends on the size of the portal and the relation of the metastatic node to the primary lesion, and on the possibility of including the two within a single radiation beam. When metastatic nodes are treated through separate portals, 4 to 5 cm. in diameter, 7,000 to 8,000 r may be given over a period of three weeks (200 to 250 kilovolts, target-skin distance, 35 cm.; filter, 0.5 to 1 cm. of copper), supplemented by radon seeds (often given in fractions) in doses of 10 to 20 millicuries, depending on the size of the node. In the present series, 2 patients with metastases (proved by aspiration biopsy) were treated by irradiation alone and have survived five years without recurrence.

If metastases from epidermoid carcinoma of the palate occur at an interval after control of the primary lesion, the method of treatment is optional and may be either by irradiation or by neck dissection. The choice of neck dissection rather than of irradiation might be based somewhat on the position of the primary lesion and on whether the metastatic nodes are unilateral or bilateral. If such late metastases are

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forming neck dissection only when cervical lymph nodes are palpably involved, but he recommended an attempt to obtain regression by irradiation of the involved nodes before resorting to surgical removal.

22. Martin, H. E.; Munster, H., and Sugarbaker, E. D.: Cancer of the Tongue, Arch. Surg. **41**:888 (Oct.) 1940. Martin and Sugarbaker.[19a]

bilateral or if the primary lesion was in the midline, indicating the possible development of bilateral nodes, the treatment should usually be radiologic rather than surgical. For late unilateral and homolateral metastases from a primary lesion not involving the midline, neck dissection is usually the preferable method and should be complete, extending down to the clavicle. In the present series neck dissection was successfully performed in 2 cases.

For cervical metastases from adenocarcinoma of the palate, which is always radioresistant, radiation therapy is not so useful as it is for epidermoid carcinoma. If the metastatic node is small (1 to 1.5 cm. in diameter), cancer-lethal radiation can be given without any particular difficulty by using a combination of external irradiation and a heavy dose of radon seeds. On the other hand, when metastatic nodes from adenocarcinoma are larger or multiple, the heavy cancer-lethal dose of radiation would have to be given over such large volumes of the neck as to make it highly objectionable or even dangerous. For these reasons neck dissection rather than radiation therapy is preferable in most cases of metastasis from adenocarcinoma, even though the operation must be bilateral.[23]

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23. A patient with adenocarcinoma of the soft palate treated five years ago and not cooperating in the regularity of his follow-up examinations was found to have bilateral metastases thirty-one months after excision of the primary lesion. Bilateral neck dissection was performed in two stages seven weeks apart. On one side the sternomastoid muscle and the internal jugular vein were removed. On the other side the vein was left in place, since it was felt that due to the patient's age (61 years) the removal of both internal jugular veins might be risky. It is probable, however, that the second vein could have been removed without any untoward result, because during a period of about half an hour near the close of the operation an assistant compressed the remaining internal jugular vein with his fingers and the patient seemed to suffer no marked ill effects, although during the compression the face became moderately cyanotic and venous bleeding from the upper portions of the wound was rather profuse. At the close of the operation the pressure was released. At the time of writing the patient has survived sixteen months without recurrence. The remaining internal jugular vein is still patent and at the present time may be occluded by digital pressure without any sign of venous congestion either in the cerebral cortex or in the subcutaneous tissues of the head.

There is little discussion in the literature as to either the safety or the advisability of removing both these vessels in bilateral neck dissection. Tailhèfer[24] stated that he had safely removed them in a few cases, with an interval of about a month between operations, but he does not consider it advisable as a rule. So far as I can learn, Crile has not mentioned it in any of his publications. In a personal discussion of this question, Jovin told me that one of his colleagues in Bucharest, Rumania, had removed both internal jugular veins in several cases without incident.

24. Tailhèfer, A.: Traitement chirurgical des adénopathies du cancer de la langue. Résultats éloignés, Mém. Acad. de chir. **62**:975, 1936.

COMPLICATIONS

Pain.—Cancer of the palate is not a painful disease except in the advanced stages, when sepsis and necrosis occur in large volumes of heavily irradiated tissue. Intractable pain is likely to be a complication when persistent attempts are made to control the radioresistant mixed tumors or adenocarcinomas of the palate by irradiation, so that there is a breakdown of normal as well as of neoplastic tissue. If the proper method of treatment is selected in the beginning, many tragic consequences of ill advised radiation therapy may be avoided.

The sensory nerve supply of the hard palate comes entirely from the second division of the fifth cranial nerve; that of the soft palate, from this source and also from the ninth cranial, or glossopharyngeal, nerve. Neurolysis of the second division by injection of alcohol should be an effective means for the relief of pain from lesions of the hard palate, but at the Memorial Hospital this procedure has proved disappointing in comparison with neurolysis of the third division. It has been the experience in that institution that the second division is more difficult to locate by the exploring needle and that even though anesthesia is obtained, the pain is likely to persist. In treating painful lesions of the soft palate I have in several instances exposed and sectioned the ninth cranial nerve in the neck. This procedure has also proved disappointing, mainly because painful lesions of the soft palate almost always extend into other nerve distributions (fifth, seventh and tenth). The most effective measures for relieving pain from palatal tumors are, first, the avoidance of irradiation of the adenoid tumors, second, the use of the smallest and most efficient portals in the irradiation of epidermoid carcinoma, and, third, the hygienic care of radiation reactions.

When intractable pain occurs, as it almost inevitably does in the later stages of uncontrolled cancer, codeine in doses of ½ grain (0.03 Gm.) with 10 grains (0.65 Gm.) of acetylsalicylic acid should be used as long as this prescription is effective; morphine should be reserved, if possible, until the life expectancy is not over a month or two.

Radionecrosis and Osteomyelitis.—These two complications are usually associated and result from the same cause. In the hard palate the bone is covered by a thin layer of soft tissue or tumor, the destruction of which by cancer-lethal radiation leaves devitalized bone exposed. Once an area of heavily irradiated bone has been exposed, spontaneous healing never occurs until after sequestration. For this reason the surgical removal by cautery and chisel of operable epidermoid carcinoma of the hard palate is often the method of choice. The advisability of surgical removal of adenocarcinoma in all cases has already been stressed. Even though a portion of the bone is removed surgically, the defect in the palate opening into the antrum or nasal cavity is usually smaller

than that which occurs following sequestration of bone after cancer-lethal irradiation. With surgical removal, healing of the edges occurs earlier and is more satisfactory, and the period of convalescence is considerably shortened. When radio-osteomyelitis occurs in the hard palate, it is usually preferable to remove the necrotic bone widely so as to promote more rapid healing and relief of symptoms.

The incidence of radionecrosis in the soft palate is much reduced if the radiation is given efficiently, that is, by using the smallest practicable portal and employing the peroral route whenever possible for at least part of the treatment, with supplementary interstitial irradiation in practically all cases, the seeds being implanted under as sterile conditions as can be obtained in this infected area. Radionecrosis in the soft palate is best treated by exercising scrupulous hygienic care, gently removing the slough by traction and clipping with scissors, spraying the base of the wound with a solution of sodium hypochlorite and frequently (every two or three hours) giving irrigations of an alkaline saline solution. As in all necrotic wounds of the oral cavity, there is gross anaerobic saprophytic infection, and the application of an oxygenic preparation, such as zinc peroxide (as developed by Meleney[25]), is always beneficial. In 32 patients of the present series (28 per cent of those treated by irradiation) there was some degree of radionecrosis and/or radio-osteomyelitis. In most cases these complications followed heavy interstitial dosage. If not too extensive in the palate, radionecrosis is not of serious consequence and seldom leads to fatal complications. Five of these patients remained alive and well for over five years.

Hemorrhage.—One of the occasional concomitants of radionecrosis in the palate is hemorrhage. The palate (hard and soft) does not contain arterial branches large enough to cause serious hemorrhage by erosion within the palate itself. When the radionecrosis or erosion by tumor extends into neighboring structures (lateral pharyngeal wall, tonsillar region), serious bleeding may occur from the erosion of larger vessels. In most of these areas immediate control of the hemorrhage can be effected by tamponage with a gauze pack held by the finger or forceps. Ligation of the external carotid artery on the affected side should be performed immediately. This vessel is best exposed by an incision along the upper anterior border of the sternomastoid muscle, which with the internal jugular vein is retracted posteriorly; by blunt dissection the bifurcation of the common carotid artery is exposed, and the external carotid artery is tied with a fine steel wire ligature. Any form of catgut ligature applied to the external carotid artery will be absorbed and the vessel recanalized within a few days or weeks. In the present series there was hemorrhage in 11 cases (11 per cent of the series). In 5 of these ligations were

25. Meleney, F. L.: Treatment of Traumatic Wounds with Zinc Peroxide, New York State J. Med. **39**:2188, 1939.

performed. There was only one immediate fatality from hemorrhage, but all these patients eventually succumbed to extensive disease. The occurrence of hemorrhage therefore indicates that the growth is far advanced and the prognosis poor.

Palatal Defects and Prostheses.—After removal of tumors of the hard palate by cautery and chisel or after radio-osteomyelitis and sequestration or removal of devitalized bone, defects of the palate opening into the antrum and/or the nasal cavity are common. These defects are similar in nature to those which occur less frequently with cancer of the gum. They produce marked functional disabilities, both in speech and in eating and drinking.

Most of these disabilities can be completely relieved with only moderate difficulty by the construction and use of prostheses (fig. 6 *D*). If a few sound teeth can be preserved in the upper jaw, such devices can be held firmly in place. When such a defect occurs in an edentulous upper jaw, the retention of the appliance constitutes a more difficult mechanical problem but one which can usually be solved by a dentist experienced in the construction of such devices. Dr. Andrew Ackerman, attending dental surgeon at the Memorial Hospital, has published a detailed description of the construction of such prostheses.[26]

Defects in the soft palate are difficult to repair, an additional reason why epidermoid carcinoma requiring the removal of the entire soft palate should be treated by irradiation rather than by surgical excision. In the removal of an adenocarcinoma or a mixed tumor of the soft palate an effort should be made not to perforate the mucous membrane on the upper surface of the palate; and when the growth occurs near the free edge the line of dissection should be as close to the tumor as safety will permit, in order to avoid a loss in continuity of the structure.

In radionecrosis or deep sepsis of the soft palate, the action of the complicated system of the intrinsic musculature is interfered with; as a result the mobility of the structure is reduced or completely lost, so that deglutition is difficult and speech is altered. In some cases the healing and scarring following the removal of a large tumor produce a retraction of the free edge of the soft palate, resulting in some change in the speaking voice and in some difficulty in swallowing liquids, which tend to enter the nasal cavity. When a defect of the hard palate also involves to even a slight extent the soft palate, the construction of a prosthesis is difficult, since the leakage of fluids into the nasal cavity tends to occur at the posterior margin of the defect, where the movable edge of the soft palate will not remain in close approximation to the device. When a large portion of the soft palate is lost, Ackerman has

26. Ackerman, A. J.: The Dental Care Before, During and After Treatment for Intraoral Cancer, Arch. Clin. Oral Path. **3**:141, 1939.

in some cases obtained marked relief from difficulties in speech and deglutition by the use of a device which partly plugs the opening between the oral and nasal pharynxes. In 3 cases in which a mixed tumor of the hard palate was surgically removed, the patient obtained complete relief from the attendant disability by wearing such a prosthesis.

END RESULTS AND PROGNOSIS

The cure rate in the present series of 93 cases of malignant tumor of the palate is given in table 3. Fourteen patients were lost track of or died of other causes after at least a year's freedom from disease, and their cases may be properly considered indeterminate. Of the 79

TABLE 3.—*Five Year End Results of Treatment of Cancer of the Palate at the Memorial Hospital from 1929 to 1936, Inclusive*

This series consists of all patients with histologically proved cancer of the palate, both early and advanced, admitted during the specified period. Only those are excluded who, for any reason, were unable to return for treatment, palliation and observation in the outpatient department and those who were lost track of within the first month after no more than one or two visits, "clinic shoppers."

Total number of patients		93
Indeterminate group:		
Dead as a result of other causes, without recurrence	13	
Lost track of, without recurrence	1	
Total number of indeterminate results		14
Determinate group (total number minus those of indeterminate group)		79
Failures:		
Dead as a result of cancer	55	
Lost track of with disease (probably dead)	4	
Living with recurrence	2	
Total number of failures in treatment		61
Successful results (free from disease after five years or more)		18
Net rate of five year cures: successful results divided by number of determinate results (18/79)		23%

patients whose cases are classified as determinate, all observed at least five years, 18 are alive without recurrence, giving a net five year cure rate of 23 per cent.

The prognosis for cure of tumors of the palate is influenced by a number of factors, of which the principal ones are given in table 4. The most significant single prognostic factor is the histologic variety of the growth, as is shown by the respective cure rates for epidermoid carcinoma (19 per cent) and adenocarcinoma (40 per cent). In 8 cases of mixed tumor of the palate not included in table 4, the cure rate was 100 per cent. It is obvious from this table that the variations in prognosis for the minor groups—selected by age, sex and various other factors—are determined largely by the difference in the relative incidence of adenocarcinoma and of epidermoid carcinoma. Since the number of cases of each of these two types of malignant tumor of the palate is not large, the two groups have been combined for some of the prognostic

calculations. Since all the patients with mixed tumors survived, this group is not included in the calculations of the prognosis.

Little discussion can be found in the literature regarding the prognosis of palatal tumors except in Ahlbom's [5] monograph. He reported permanent cures (five years or more) of 25 per cent of all malignant tumors of the mucous and salivary glands (including the

TABLE 4.—*Factors Influencing the Five Year Cure Rate for Cancer of the Palate in Seventy-Nine Patients with Determinate Results, Observed at the Memorial Hospital from 1929 to 1936, Inclusive*

	Total No. of Patients	No. of Five Year Cures	Percentage of Five Year Cures
Age in years:			
Below 40	4	1	25
40 to 49	11	4	36
50 to 59	21	6	29
60 and over	43	7	16
Sex:			
Male	64	12	19
Female	15	6	40
Size of primary lesion:			
Under 1 cm.	2	1	50
1 to 1.9 cm.	7	4	57
2 to 2.9 cm.	7	4	57
3 to 3.9 cm.	17	5	29
4 to 4.9 cm.	15	2	13
5 cm. and over	15	1	7
Not stated or scar present	16	1	6
Position of lesion:			
Hard palate	23	8	35
Soft palate	50	10	20
Junction between hard and soft palate	6	0	0
Metastases:			
None on admission	42	17	40
None at any time	30	15	50
Cervical involvement on admission	36	1	3
Cervical involvement after admission	10	2	20
Systemic involvement after admission	3	0	0
Sometime during course	49	3	6
Histopathologic structure:			
Adenocarcinoma	15	6	40
Squamous carcinoma grade I	12	7	60
Squamous carcinoma grade II	36	4	11
Squamous carcinoma grade III	7	1	14
Squamous carcinoma ungraded	2	0	0
Transitional cell carcinoma grade II	4	0	0
Transitional cell carcinoma grade III	1	0	0
Melanoma	1	0	0
Rhabdomyosarcoma	1	0	0

parotid and submaxillary salivary glands). That figure cannot be compared directly with those given in this report, since the groups are not of similar composition. Ahlbom emphasized the fact that the prognosis of malignant salivary gland tumors is not as hopeless as many have believed. He also stated that the malignant tumors of salivary gland origin in the palate have a worse prognosis than these tumors in other regions, an observation which is in agreement with the findings at Memorial Hospital.

Age.—The number of malignant palatal tumors in patients under the age of 40 is too small to allow definite conclusions. The cure rates for patients in the fifth and sixth decades, averaging over 30 per cent, are in marked contrast to the 16 per cent cure rate for patients over the age of 60. The better prognosis in the younger age groups undoubtedly is due to the greater incidence of the more curable adenocarcinomas in the younger age group; in the group over the age of 60 there is a preponderance of the more malignant epidermoid carcinoma, and the mortality among these older patients from complications of treatment is higher. Such a trend, from the same cause, is apparent with all forms of intraoral cancer.

Sex.—As with most forms of intraoral cancer, the prognosis of cancer of the palate is better in females (40 per cent cure rate) than in males (19 per cent). Part of this trend may be due to the fact that cancer in the female is more radiosensitive than cancer in the male. However, this would operate only with regard to the epidermoid carcinomas which were treated by irradiation. It may be significant that when the figures are broken down further, of the 15 patients with adenocarcinoma, only 2 of the 7 males survived five years (28 per cent), as opposed to 4 of the 8 females (50 per cent); this suggests that the better prognosis of cancer in females is related not to radiosensitivity alone but also to other sex differences.

Metastases.—As with all forms of cancer, the capacity to metastasize is the predominating factor in the malignancy of palatal tumors. In other words, no matter what the clinical behavior of the primary tumor, its capacity to destroy life is not great until it has metastasized.

When metastases were present on admission, the cure rate of the malignant tumors was only 6 per cent, a figure approximately the same as the cure rate of cancer of the tongue with metastases (8 per cent). The low cure rate in patients admitted with metastases is determined mainly by the significant fact that this group includes the patients admitted in the advanced stages of the disease, practically all of whom have metastases. In the present series the patients with palatal cancers in whom metastases developed after admission had a cure rate of 8 per cent, which is only slightly better than the cure rate of all patients with metastases (6 per cent).

In those patients in whom metastases do not occur at any time during the course of the disease, the chance of cure is 50 per cent (eight times that in patients with metastases). In 18 patients with bilateral metastases there was 1 cure (5 per cent).

Size of the Primary Lesion.—As might be expected, the cure rate of malignant tumors of the palate is considerably influenced by the size of the primary lesion, decreasing from 55 per cent for lesions up to 2 cm. in diameter to 7 per cent for those 5 cm. or more in diameter. This

decrease is caused not only by the greater difficulty in curing the larger lesions but also by the higher proportion of metastases from the larger lesions.

Position of the Lesion.—The difference in the cure rate with respect to the site of the lesion is due mainly to the preponderance of epidermoid carcinoma in the soft palate (77 per cent of the malignant tumors in this area) as compared with the hard palate (23 per cent), where there is a greater proportion of the less malignant adenocarcinoma (57 per cent). Other reasons for the greater comparative malignancy of growths in the soft palate may be that anaplastic epidermoid carcinoma is more apt to occur in this structure adjacent to the nasopharynx and that metastasis is favored by the mobility of the soft palate.

Histopathology.—As previously mentioned, the histologic form of the growth is one of the most significant factors in prognosis. The cure rate of adenocarcinoma (40 per cent) is twice that of epidermoid carcinoma (19 per cent). It is well known that all adenocarcinoma of the oral cavity and, as a matter of fact, any form of adenocarcinoma may recur at long intervals (ten, fifteen or twenty years after apparent control) and that such recurrence is not nearly so frequent with epidermoid carcinoma. Although at the Memorial Hospital it is conceded that with adenocarcinoma the follow-up period of five years is sometimes insufficient, still in order to obtain a reasonable basis for calculation we have used a five year period of control for the whole group. Watson [2] called attention to the fact that in 4 cases of adenocarcinoma of the oral cavity there was recurrence after ten years. In some cases of apparent late recurrence the possibility of multiple primary lesions of adenocarcinoma must always be considered.

Epidermoid carcinoma of the palate tends to follow the same clinical course as tumors in adjacent sites—palatine tonsil, base of tongue, extrinsic larynx—that is, rapid growth and early metastasis. Adenocarcinoma of either the hard or the soft palate tends to progress slowly in a manner resembling that of the benign mixed tumors, the main difference being that adenocarcinoma metastasizes and mixed tumors do not. The influence of tumor grading is also shown under this heading, but the number of cases is too small to permit any definite conclusions. As might be expected, the cure rate is 100 per cent for the benign mixed tumors.

SUMMARY

Tumors of the palate, both malignant and benign, are discussed from the standpoint of etiology, clinical course and treatment, and details of treatment are discussed.

The net five year cure rate in 93 cases of cancer of the palate was 23 per cent.

737 Park Avenue.

MALIGNANT LESIONS OF THE STOMACH

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The most frequent site of cancer in the gastrointestinal tract is the stomach, and, as encountered at the Mayo Clinic, this type of cancer affects males three and a half times as frequently as it affects females. The treatment of cancer of the stomach since Billroth first removed the lesion successfully by gastric resection in 1881 has been removal by surgical methods. Although the results of treatment of localized cancer of the stomach of low grade malignancy have been as satisfactory as those of treatment of cancer of the colon, the greater frequency of highly malignant lesions in the stomach and the large number of cases in which the disease does not produce symptoms indicative of gastric neoplasm until late in the course of the disease explain the larger percentage of inoperable malignant lesions of the stomach as compared with inoperable malignant lesions of the colon. The hopeful aspect of the surgical treatment of cancer of the stomach has been that in 28.9 per cent (31.9 per cent, when the figure is adjusted for the normal death rate) of cases in which the lesions were removed surgically, irrespective of the grade of malignancy or involvement of the regional lymph nodes, the patients were living and well five years or more after operation. If the survival curve is compared with the survival curve for the normal population, it is noted that the two curves are practically parallel for the period of more than five years beyond the survival of patients subjected to gastric resection. One of the most hopeful aspects of the study of patients at the Mayo Clinic has been the fact that in cases in which there was no extension of carcinoma or involvement of the lymph nodes, 45 per cent of the patients lived five years or more after leaving the hospital.

Computed on the basis of Broders' index of malignancy, which is dependent on the proportionate number of malignant and normal cells in any typical microscopic field, the five year survival rate after resection was 86.2 per cent in cases in which the lesion was graded 1 (the differentiation ranging from 75 to 100 per cent), 58.8 per cent in cases in which the lesions were graded 2 (the differentiation ranging from 50 to 75 per cent), 30.2 per cent in cases in which the lesions were

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From the Division of Surgery, the Mayo Clinic.
The first Walter E. Hering lecture, delivered at the Hahnemann Medical College and Hospital of Philadelphia, Nov. 18, 1941.

graded 3 (the differentiation ranging from 25 to 50 per cent) and 23.3 per cent in cases in which the lesions were graded 4 (the differentiation ranging from 0 to 25 per cent).

AGE AND SEX AS FACTORS IN SURVIVAL AND RESECTABILITY

The youngest patient (including both sexes) on whom partial gastrectomy was performed was 18 years of age. The oldest man was 88 years old, and the oldest woman was 81 years old. It is commonly believed that malignant lesions occurring among younger patients are of a more fulminating character than those which afflict older persons and that the results of treatment of carcinoma among younger patients are therefore considerably poorer than the results obtained with patients of the older age groups. Results of studies of patients at the Mayo Clinic, however, make possible a much more optimistic view, for after surgical removal of malignant lesions of the stomach among patients less than 40 years of age, the five year survival rate was 25.1 per cent (26.0 per cent, when adjusted for the normal death rate) in contrast to the survival rate of 29.7 per cent for patients who were 40 to 49 years of age (31.2 per cent, when adjusted for the normal death rate). The five year survival rate for patients 50 to 59 years of age was 29.2 per cent (32.2 per cent, when adjusted for the normal death rate); the rate for patients 60 to 69 years of age was 28.9 per cent (35.8 per cent, when adjusted for the normal death rate), and that for patients 70 years or older was 29.8 per cent (49.3 per cent, when adjusted for the normal death rate). On the basis of these figures it can be seen that for patients less than 40 years of age who have removable malignant lesions of the stomach, the five year survival rate, although it is somewhat less than that for patients in the older groups, nearly approximates it.

This, I believe, is important, especially since a study of the ratio of gastric resection to the total number of cases of gastric carcinoma in age groups by decades shows that the total percentile average (for the whole series) was 25.5, as compared with a percentile average of 26.7 for patients less than 30 years old, 27.7 in the age group of 30 to 39 years, 25.4 in the age group of 40 to 49 years; 27.4 in the age group of 50 to 59 years, 24.4 in the age group of 60 to 69 years and 20.0 in the age group of more than 70 years.

The rate of resectability among patients less than 30 years of age was 38.7 per cent; among patients 30 to 39 years, it was 41.9 per cent; among patients 40 to 49 years, it was 43.4 per cent, and among patients 50 to 59 years, it was 45.3 per cent. The average rate of resectability for patients in all age groups was 44.4 per cent.

It must be remembered, however, that a relatively small proportion of patients (90) were less than 30 years of age; but 660 patients were

between 30 and 39 years of age; 2,217 were between 40 and 49 years of age; 3,622 were between 50 and 59 years of age; 3,404 were between 60 and 69 years, and 897 were more than 70 years of age.

I should like to call attention to the fact that both the surgical rate and the rate of resectability were higher among females than among males and that the hospital mortality rate was considerably lower among females, being 12.8 per cent for gastric resection as compared to 17.3 per cent for gastric resection in males. The five year survival rate, on the other hand, apparently was the same for both males and females, and this was true regardless of the type of surgical procedure that was performed.

FIVE CRITERIA OF LIVINGSTON AND PACK

Livingston and Pack,[1] in their most interesting presentation of published data on the surgical treatment of cancer of the stomach, suggested that "for a study of end results the subject of gastric cancer as a whole must be broken down into several definite subgroups, each of which has a technical significance of its own and an importance which is lost to view unless the particular subgroup is unmistakably identified." These groups include: (1) the total number of patients observed in any given series of cases; (2) the total number of patients who come to operation; (3) the number who undergo resection or gastrectomy; (4) the number who survive resection (immediate survivors) or the number who undergo resection minus the number of those who succumb after resection; (5) the long term survivors, or those still living at a fixed end period, who constitute what might be considered a group definitely cured.

Following this suggestion, my colleagues, Dr. H. K. Gray and J. T. Priestley and I,[2] with the assistance of Dr. Everett Lewis (assistant in surgery), extracted data from the records of all patients with malignant lesions of the stomach who were seen at the Mayo Clinic during the years 1907 to 1938, inclusive. Follow-up data were obtained concerning 98 per cent of the patients living. In this period 11,000[3] patients who had malignant lesions of the stomach were examined at the clinic. Of the 11,000 patients with a malignant process of the stomach, 6,352 underwent operations; 2,840 were subjected to resection. The average mortality rate for partial gastrectomy was 16 per cent.

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1. Livingston, E. M., and Pack, G. T.: End Results in the Treatment of Gastric Cancer: An Analytical Study and Statistical Survey of Sixty Years of Surgical Treatment, New York, Paul B. Hoeber, Inc., 1939.

2. Walters, W.; Gray, H. K., and Priestley, J. T.: Malignant Lesions of the Stomach: Results of Treatment in the Years 1907 to 1938, Inclusive, Tr. West. S. A. **50**:200-218, 1940; Malignant Lesions of the Stomach: Importance of Early Treatment and End-Results, J. A. M. A. **117**:1675-1681 (Nov. 15) 1941.

3. Of these, 10,890 had carcinoma, and 110 had sarcoma.

INCIDENCE OF SARCOMA

It might be of interest to call attention to the fact that in the series of patients (6,352) who had malignant lesions of the stomach and who were operated on, 110, or 1.7 per cent, had sarcoma. The most interesting statistical difference between sarcoma and carcinoma is apparent in the distribution in age. Of the patients who had sarcoma, 24.5 per cent were less than 40 years of age, whereas only 6.9 per cent of those who had carcinoma of the stomach were less than 40 years of age. Survival rates accompanying gastric resection for sarcoma closely paralleled those accompanying gastric resection for carcinoma.

POSSIBLE IMPROVEMENT OF RESULTS

In studying the points which have been mentioned thus far, we were interested not only in determining the results of treatment but also in endeavoring to learn whether it would be possible to improve the results of treatment, first, by earlier recognition of the malignant gastric neoplasm before extension occurred and, second, by determining whether preexisting lesions thought to be benign had preceded the development of the malignant lesion.

Indefinite Type of Dyspepsia.—One of the difficulties encountered in early recognition of the symptoms of cancer was the frequency with which an indefinite type of dyspepsia was associated with the lesion until such a time as obstruction or hemorrhage occurred. This indefinite type of dyspepsia was secondary to a disturbance of motility, characterized for the most part by a sensation of fulness or distress after eating, usually associated with loss of weight. However, obstruction as a first symptom of gastric carcinoma was present in 52 per cent of the cases. Bleeding occurred as the first symptom in only 1.3 per cent of the cases of gastric carcinoma. These percentages refer to patients who underwent an operation of any kind and include resection as well as other procedures.

Ulcerlike Symptoms.—The most likely source of diagnostic error was encountered among those patients who had symptoms which are commonly associated with benign ulcer of the stomach and the duodenum. Surprisingly enough, a third of the patients had such a history. In approximately the same proportion (a third) of the patients, the ulcerous type of symptom was the first.[4] Of even greater importance was the fact that when patients who had this so-called ulcerous type of history followed a medical regimen for ulcer, 80.6 per cent achieved a temporary effective response with relief of pain—suggesting, therefore,

4. Characterized by a burning or gnawing pain in the epigastrium occurring two to three hours after eating which is relieved by food and sodium bicarbonate and by emptying the stomach.

benign ulceration. Several years ago, I said it was my impression that approximately 20 per cent of the patients operated on for cancer of the stomach had received treatment for suspected benign ulcer before a roentgenogram was made which revealed the gastric lesion to be malignant. The corollary of this, it seems to me, is that no matter how typically a patient's history simulates that of a patient who has benign ulcer, the lesion should not be assumed to be benign until it is demonstrated roentgenographically to be situated in the duodenum.

In a recent group of cases reported before the Society of Clinical Surgery in 1941, Stout [5] called attention to a type of gastric carcinoma which he said appears to be encountered with increasing frequency in resection of the stomach as performed at the Presbyterian Hospital and Sloane Hospital for Women in New York. The carcinoma is of the infiltrating type, involving the mucous membrane and the submucosa of the stomach, and frequently has an origin in gastric ulcer. Many of these lesions were situated along the lesser curvature of the stomach and escaped attention by the roentgenologist because of spasm of the pylorus which produced pyloric obstruction. I, too, have seen lesions of this type, and in many instances the patients have had a long history of so-called ulcer dyspepsia, a history which sometimes covers a period as long as eight years. In such cases, because of the pyloric obstruction present, the diagnosis has been duodenal ulcer.

Since attention has been called to the important part played by gastric ulcer in the treatment of cancer and to the possible error of diagnosing a cancerous gastric ulcer as a benign lesion, it may well be asked, "Why have not all chronic gastric ulcers been operated on?" Experience has shown that many gastric ulcers, usually those of small size and of short duration, may heal if a properly carried out medical regimen in the hospital is instituted; in a few cases large chronic ulcers may heal, at least seemingly so, only to recur later. In my experience many such ulcers, when they have been operated on later, have proved to be malignant. The argument is sometimes advanced that the risk of removal of chronic gastric ulcer is greater than the possibility of the ulcer being malignant or of its becoming malignant. With this I take sharp issue, for the risk associated with removal of gastric ulcer should not exceed a maximum of 5 per cent, and it is possible to operate on a large series of patients who have gastric ulcer and achieve a mortality rate of considerably less than 5 per cent. In point of fact, partial gastrectomy was performed at the Mayo Clinic in 89 cases in 1939, with a mortality rate of 2.2 per cent. This particular series (89 cases) constituted 56 per cent of all patients having gastric ulcer examined at the clinic. In 1940,[6] partial gastrectomy

5. Stout, A. P.: Unpublished data.

6. Gray, H. K.; Walters, W., and Priestley, J. T.: Report of Surgery of the Stomach and Duodenum for 1940, Proc. Staff Meet., Mayo Clin. **16**:721-727 (Nov. 12) 1941.

for gastric ulcer was performed in 88 cases, with 1 death. Excision of the ulcer or gastroenterostomy or both performed in 17 cases of gastric ulcer resulted in no deaths. Patients were selected carefully, and partial gastrectomy was performed only when the nature of the lesion and the condition of the patient warranted this procedure. From the standpoint of the possibility of recurrence of ulceration, I have never seen a benign gastric ulcer or a gastrojejunal ulcer return after partial gastrectomy in which half or more of the stomach was removed. On the other hand, recurrence of gastric ulceration does occur after medical treatment, but the difficulty of distinguishing between disappearance of the crater of the ulcer resulting from filling in by granulation tissue as against the extension over the crater by the malignant portion of the lesion when viewed roentgenographically has been commented on by Schindler.[7] This difficulty has been a serious source of error in the treatment of some of the patients, in that the crater disappeared, as did the pain and the blood in the stools, when the patients followed a medical regimen for ulcer. Hence, the lesion was thought to be benign. When symptoms returned or an ulcerous lesion reappeared in the gastric roentgenogram, surgical treatment was advised. At operation in some cases, the lesion proved to be malignant, and in some cases it was inoperable.

I wish to emphasize, therefore, the fact that seeming disappearance of a gastric ulcerating lesion when it is viewed roentgenographically, with relief of symptoms, is not *always* indicative of benignancy, for the reasons I have stated. Patients who have such a condition should be kept under observation, and examinations should be carried out frequently for a period of two years. Supplementing the roentgen report of disappearance of the gastric lesion, a gastroscopic examination should be carried out to confirm such an impression.

Assistance from the Roentgenologist.—When the lesion is situated in the stomach, a source of error which the roentgenologist has frequently emphasized may arise, namely, a definite percentage of carcinomatous ulcers have the roentgen appearance of benign ulcer. In 10 per cent of the cases in which resection was performed for gastric carcinoma, the lesions were reported by the roentgenologists to be gastric ulcer. In 1939,[8] of 131 cases in which gastric resection was performed for malig-

7. Schindler, R.: Early Diagnosis of Cancer of the Stomach: Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays, J. Nat. Cancer Inst. **1**:451-471 (Feb.) 1941.

8. Gray, H. K.: Report on Surgery of the Stomach and Duodenum, 1939: Gastric Ulcer, Proc. Staff Meet., Mayo Clin. **15**:710-711 (Nov. 6) 1940. Priestley, J. T.: Report of Surgery of the Stomach and Duodenum, 1939: Duodenal Ulcer, ibid. **15**:707-709 (Nov. 6) 1940. Walters, W.: Report on Surgery of the Stomach and Duodenum, 1939: Malignant Lesions of the Stomach, ibid. **15**:712-717 (Nov. 6) 1940.

nant lesion of the stomach at the Mayo Clinic, the roentgenologist had reported the gastric lesion to be a gastric ulcer in 9 cases, or 7 per cent. At the clinic, in the period of 1939 and 1940, in 237 cases in which the diagnosis was gastric ulcer and in which the patients underwent operation, 19 of the patients, or 8 per cent, were found to have malignant gastric lesion.

The ability of roentgenologists to recognize the presence of gastric lesions, when they are present, in from 98 to 99 per cent of the cases is a truly great achievement, especially when they are able to recognize lesions which in many instances are no larger than a thumbnail. In the series on which this paper is based, in the cases in which partial gastrectomy was performed for carcinoma (2,772), although the presence of a gastric lesion was demonstrated in 99 per cent of the cases, in only 75.3 per cent was the lesion reported unqualifiedly as being malignant.

Studies of Gastric Acidity.—With the large group of patients having histories suggesting benign ulcer and with the definite possibility that the error of reporting cancerous ulcer as benign ulcer roentgenographically may occur, it seems that studies of gastric acidity may be helpful in arriving at the differential diagnosis. The significance of a gastric lesion associated with achlorhydria (indicating that the lesion is malignant) is well known to all. Yet, only 51.4 per cent of the patients on whom partial gastrectomy was performed had achlorhydria, and achlorhydria was present in practically the identical percentage of those for whom only palliative procedures could be carried out. In other words, 50 per cent of the patients operated on for carcinoma of the stomach had some amount of free hydrochloric acid, and in comparing the values for hydrochloric acid it was noted that in members of both groups, namely, those who underwent resection as well as those for whom palliative procedures were carried out, free hydrochloric acid was present, ranging from 1 to 29 degrees in approximately 30 per cent of the cases; from 30 to 49 degrees in approximately 15 per cent of the cases, and 50 degrees or more in approximately 5 per cent of the cases. To express it differently, approximately 20 per cent of the patients operated on for carcinoma of the stomach had a free hydrochloric acid content (Töpfer's method) of more than 30 degrees. It is apparent, therefore, that the presence of hydrochloric acid in the gastric contents does not exclude the possibility that the gastric lesion is malignant.

Gastroscopy.—The development of gastroscopy in the United States in the past few years has added materially to the recognition and observation of intragastric lesions. The method has been helpful also in decreasing that percentage of roentgenologic error which arises because of the difficulty of visualization and identification of lesions situated high in the posterior wall or the fundic end of the stomach. Gastroscopic

examination should be carried out in every case in which the clinical picture would lead the physician to suspect the possibility of an intragastric lesion after an uncertain report has been obtained subsequent to roentgenoscopic and roentgenographic examination of the stomach. The procedure is helpful also in following the course of the patients by direct observation of the gastric ulcer when medical treatment has been instituted as a trial measure.

Medical Treatment.—It is apparent, therefore, that much care must be exercised in the selection of patients for medical treatment when they have been reported as having benign gastric ulcer, in view of the approximate 10 per cent of the cases, previously mentioned, in which patients supposed to have benign lesions were found at operation to have malignant lesions. In statistics from other clinics the incidence of malignant changes in gastric ulcer has been stated to be from 10 to 20 per cent. Sir James Walton [9] stated that the figures of Stewart [10] are now generally accepted, namely, that 9.5 per cent of chronic gastric ulcers become carcinomatous and that 17 per cent of carcinomas originate in chronic gastric ulcer. Katsch [11] reported an incidence of malignant change of 20 per cent, and Finsterer [12] found that in 532 cases in which resection had been performed for gastric ulcer, the ulcer was carcinomatous in 141, an incidence of "20.9 per cent."

THE ROLE OF BENIGN GASTRIC TUMORS, INCLUDING POLYPS

The most frequent benign tumors of the stomach are small fibroadenomas. These vary in size, frequently are small and may produce no symptoms until bleeding occurs. Other benign gastric tumors are leiomyoma, fibromyoma, neurofibroma and adenomyoma.

The symptom most frequently produced by benign tumor of the stomach is bleeding. Several of the patients had no evidences of an intragastric lesion until during the course of the examination designed to rule out such lesions as a source of the anemia which had been noted, the presence of an unsuspected gastric or colonic polyp or polyps was discovered on roentgen examination. Many of the patients had been treated for suspected primary anemia.

Some of the pedunculated gastric polyps prolapse at times through the pylorus, producing various types of obstructive dyspepsia. In some cases the bleeding may occur so gradually that the patient's first symp-

9. Walton, J.: Carcinoma of the Stomach, Lancet **1**:1101-1107 (May 16) 1936.
10. Stewart, cited by Walton.[9]
11. Katsch, cited by Hurst, A. F.: Carcinoma of the Stomach, Lancet **2**:1455 (Dec. 18) 1937.
12. Finsterer, H.: Malignant Degeneration of Gastric Ulcer, Proc. Roy. Soc. Med. **32**:183-196 (Jan.) 1939.

toms are weakness and asthenia due to secondary anemia, and a bleeding gastric lesion is recognized only on roentgen or gastroscopic examination of the stomach.

In my experience, the lesions which produce these symptoms most frequently are leiomyomas, some of which reach a large size. On April 21, 1938, I operated on a woman from whose stomach I removed a hemorrhagic degenerating leiomyoma, 12 by 13 by 9 cm. Her only symptom was weakness, but she had noticed the tumor herself by inspection and palpation of the abdomen.

Conversion into Malignant Tumor.—The tendency of some of these seemingly benign tumors to metastasize is evidenced by the case of Sworn and Cooper.[13] These observers reported the presence of hepatic metastasis in a patient with leiomyoma of the stomach. It is, of course, possible for such a lesion to degenerate and become malignant leiomyosarcoma. On June 14, 1940, I operated on a woman who had a large degenerating leiomyosarcoma, 7 by 6 by 5 cm. The presence of the tumor had been known for four years. So much bleeding had occurred from it that at one time erythrocytes had numbered 1,900,000, with a corresponding decrease in hemoglobin. The tumor was removed by partial gastric resection. She returned to the clinic for reexamination on March 3, 1941, nine months after operation; at this time her general health was excellent. The value for hemoglobin was 12.1 Gm. per hundred cubic centimeters, and there was no evidence of recurrence.

Miller, Eliason and Wright[14] reported the incidence of malignant degeneration to be 35 per cent in 23 specimens of gastric tumor subjected to careful histologic study. Brunn and Pearl[15] found that in 12 per cent of 82 collected cases malignant degeneration was reported. Rieniets,[16] while he was a fellow in surgery in the Mayo Foundation for Medical Education and Research (1940), made a comprehensive study of gastric adenoma and stated that "the relationship of gastric adenomas to adenocarcinoma is not to be interpreted in the sense that all adenomas become malignant, but the writer's study proves conclusively that these adenomas

13. Sworn, B. R., and Cooper, T. V.: Leiomyoma of the Stomach, Lancet **1**:428-429 (Feb. 19) 1938.

14. Miller, T. G.; Eliason, E. L., and Wright, V. W. M.: Carcinomatous Degeneration of Polyp of the Stomach: Report of Eight Personal Cases with a Review of Twenty-Four Recorded by Others, Arch. Int. Med. **46**:841-878 (Nov.) 1930.

15. Brunn, H., and Pearl, F.: Diffuse Gastric Polyposis: Adenopapillomatosis Gastrica; Report of Five Proven and Seven Probable Cases, Surg., Gynec. & Obst. **43**:559-598 (Nov.) 1926.

16. Rieniets, J. H.: A Comprehensive Study of Gastric Adenomas with Special Reference to Their Pathologic Anatomy, Complications, and Tendency to Malignant Transformation, Thesis, University of Minnesota Graduate School, 1940.

are potentially malignant, and the size and volume of the tumor alone are not the determining factors for malignancy but rather the cellular activity of the neoplastic process."

Indications for Removal.—It seems clear, therefore, that the indications for removal of benign tumor of the stomach are apparent; it should be removed not only because of the symptoms of bleeding and anemia which the tumor itself produces but also because of the possibility that malignant degeneration may take place, especially if the tumor contains adenomatous and myomatous tissue.

PATHOLOGIC NATURE OF THE LESIONS

In a discussion of survival rates, the most important details regarding the pathologic nature of the lesion should of course be known. While the size of the tumor varied, as might be expected, from as small as 1 or 2 cm. to as much as 9 cm. or more, it is interesting to note that the least extensive type of gastric resection, namely, local excision, occasionally was performed for lesions of small size (averaging 3.4 cm. in diameter).[17] In contrast to this were the cases in which the posterior Polya type of operation was performed; in these the average diameter of the lesions was 6.2 cm. The anterior Polya-Balfour operation was performed when the lesions were, on the average, 7 cm. in diameter, while total gastrectomy was employed for lesions 9.2 cm. or larger. It is interesting to note that among the various lesions there is a definite and progressive increase in the proportion of involvement of lymph nodes as the size of the lesion increases but that there is also a definite decrease in the value for hemoglobin as lesions increase in size. The effect of the size of the lesion on the mortality rate accompanying gastric resection is interesting, for the lesions of smaller size (3 cm. or less) were accompanied by a definitely lower mortality rate (averaging about 6 or 7 per cent). As the lesions increased in size (7 cm. or more in diameter), the mortality rate increased.

Metastasis.—In 45.3 per cent of the cases in which resection was done, metastasis was not present, while in 53.5 per cent of such cases metastasis was found in the gastric lymph nodes. Involvement of the retroperitoneal or other abdominal lymph nodes or hepatic metastasis was present in approximately 1 to 2 per cent of the cases in which resection was done. On the other hand, in those cases in which palliative operations were performed extragastric involvement of lymph nodes was present in 12.6 per cent; extragastric involvement of the liver was present in 12.8 per cent, and abdominal metastasis was present in 14.7 per cent.

17. Operations of this type for small gastric lesions, although frequent in the period preceding the advent of partial or subtotal gastrectomy, have in the last twenty-five years been used only rarely.

INDICATIONS FOR OPERATION

In many instances roentgenologists have attempted to aid the clinician and the surgeon further by expressing an opinion as to the operability of the lesion which they see roentgenographically, the operability being based, in their minds, on whether or not there seems to be a sufficient portion of normal stomach above the lesion to permit removal of the lesion with restoration of gastrointestinal continuity. For example, those lesions involving the lower half of the stomach might be considered to be operable as well as certain of those in the middle third part of the stomach. In 20 per cent of the cases in which surgical exploration was undertaken, although the lesion was considered roentgenologically to be inoperable or of doubtful operability, the lesion proved to be removable. With recognition of this error of interpretation in recent years, the percentage of patients who have undergone exploratory operation for cancer of the stomach has increased progressively. The rate of removability likewise has increased because of the willingness of surgeons to remove, if possible, every malignant gastric lesion that has not metastasized to regions from which it cannot be removed. The extent to which this may be carried is evidenced by the fact that although up to 1938, inclusive total gastrectomy had been performed 27 times, during 1937, 1938, 1939 and 1940 total gastrectomy was performed 16 times, with a mortality rate of 31.2 per cent. In 1940, total gastrectomy was performed 8 times, with 1 death. In the last few years, by means of a transthoracic approach, lesions of the lower end of the esophagus and the cardial end of the stomach have been successfully removed; the diaphragm has first been split, and then it has been resutured together around the stomach below the point of esophageal gastric anastomosis. Cases in which this procedure was successful have been reported by Phemister,[18] Ochsner [19] and me.[20]

I have previously presented some of the statistics concerning favorable results in the surgical extirpation of lesions confined to the stomach and those of a low degree of malignancy. I have also called attention to favorable results of partial gastrectomy for patients in the younger age groups, i. e., between the ages of 20 and 40 years. I should like to

18. Adams, W. E., and Phemister, D. B.: Carcinoma of the Lower Thoracic Esophagus: Report of a Successful Resection and Esophagogastrostomy, J. Thoracic Surg. **7**:621-632 (Aug.) 1938. Phemister, D. B.: The Operative Treatment of Carcinoma of the Esophagus, Illinois M. J. **79**:497-500 (June) 1941.

19. Ochsner, A., and DeBakey, M.: Surgical Aspects of Carcinoma of Esophagus: Review of Literature and Report of Four Cases, J. Thoracic Surg. **10**:401-445 (April) 1941.

20. At the time of writing, the first patient for whom this type of operation was utilized by me is in the hospital on the twenty-first postoperative day. In this case the procedure included transthoracic esophageal gastric resection and esophageal gastric anastomosis.

amplify those statements somewhat by stating that, in spite of the fact that the average age at which the patients who had cancer of the stomach were operated on in the present series was 55.5 years, 20 per cent of all patients survived for ten years; 15 per cent survived for fifteen years; 11 per cent survived for twenty years or more, and 6 per cent survived for twenty-five years or more. I wish to emphasize again that when these survival rates are compared with the normal mortality rates in the general population, it is noted that the two curves are practically parallel from the period of five years beyond the survival of the patients who survived resection.

TYPES OF OPERATION

The operation of gastric resection, referred to as partial or subtotal gastrectomy, has been established as a procedure of greatest value in the radical removal of a malignant lesion of the stomach. The reason for this is that the lower limit of extension of gastric carcinoma is the pylorus, and if the duodenum is divided below the pylorus, so that all the lower part of the stomach, including the pylorus and the gastrohepatic and the gastrocolic omentum, is removed, extension of the neoplasm beyond these areas is effectively prevented, unless extension has already occurred, as in the case of involvement of the retroperitoneal lymph vessels. By removal of part of the stomach at as high a level as is consistent above the site of the tumor and the attached omentum containing lymph nodes, the possibility of direct extension of the carcinoma to areas beyond the lesion, as well as through the intragastric lymphatic channels, is obviated.

The operations which have been most effective are those described by Polya and Balfour, which are modifications of the Billroth II operation. In the Polya operation the remaining portion of the stomach is joined to the side of the jejunum, posterior to the colon. Balfour modified the operation by advising that a longer loop of jejunum be used and that the anastomosis be made anterior to the colon. When this is done, it is usually advisable to establish enteroanastomosis between the jejunal loops to prevent gastric retention. In 24 per cent of the cases in which partial gastrectomy was done, the operation was of the anterior Polya-Balfour type, and in 46 per cent it was of the posterior Polya type, the total for both procedures being 1,923 or 2,745 cases in which partial gastric resection was carried out for carcinoma (the figure of 2,745 does not include 27 cases in which total gastrectomy was performed for carcinoma).

Generally speaking, the Polya-Balfour operation was used in those cases in which extensive resection was necessary because of the large size of the lesion.

The Billroth I operation was used only 170 times, but the mortality rate associated with it was the lowest of all such rates for the various procedures, being 11.2 per cent. The lesions for which this operation were performed were next to the smallest in size, and the five year survival rate associated with it was better than the five year survival rate accompanying the Polya type of procedure.

There was a small group of cases in which local excision of the tumor was carried out. The reason for utilization of this procedure has been explained earlier in the paper. In most of these cases, operation was carried out before the advent of the almost routine use of the Polya type of resection. As the results of treatment in these cases are examined, it is interesting to note that the average size of the lesion for which this procedure was carried out was 2.7 cm., or only a half to a third of that for which the Polya type of procedure was carried out. In addition, in approximately 53 per cent of the cases in which local excision was done, the lesions were graded 1 or 2, in contrast to lesions of grade 1 or 2 in only 25 per cent of cases in which the Billroth I operation was performed and lesions of grade 1 or 2 in only 19.4 per cent of cases in which the Polya or Polya-Balfour operation was performed. It may be said, however, that in some cases in which the tumor is small and in which the lesions are of a low degree of malignancy, wide removal of the lesion may be followed by an excellent result and hence might be indicated for elderly or debilitated patients.

Palliative Operations.—For the most part, the radical removal of neoplasms of the stomach has been considered thus far, and I have emphasized throughout this paper the relationship of the survival rate in such cases to the various factors of age, size of the lesion, sex of the patient and type of operation performed. There was, of course, a large number of cases (1,039) in this series in which gastric extension of carcinoma made complete removal of the malignant neoplasm impossible, but in which, for one reason or another (usually obstruction), palliative types of operation, such as gastroenterostomy or jejunostomy, were performed. The mortality rate accompanying palliative operations of this type almost equaled that accompanying gastric resection. A five year survival rate of 1.1 per cent was associated with the palliative operations, in contrast to a rate of 0.6 per cent associated with surgical exploration. This seems to be direct evidence in support of the viewpoint that palliative operations for inoperable, irremovable gastric neoplasm are seldom advisable.

MORTALITY RATE

In the management of complicated malignant lesions of the stomach the mortality rate is directly proportional to the experience of the surgeon and the condition of the patient. It will also depend on the extent to

which the surgeon is willing to remove large portions of the stomach for the purpose of excision of malignant lesions. For example, the risk of total gastrectomy is considerably higher than that of subtotal gastrectomy. Likewise, the operation is more difficult, and there is more possibility of postoperative complications when the lesions are large and are situated in the middle or the upper part of the stomach and have produced a considerable degree of debility as a result of obstruction, bleeding and ulceration. The average mortality rate for the series (1907 to 1938, inclusive) in which partial gastrectomy was done was 16 per cent, but in 1940, the mortality rate was 8.5 per cent in 117 cases in which this operation was carried out for cancer of the stomach.

I think it is worth while to recapitulate, somewhat, what has been said concerning those factors which influence the mortality rate. First of all, it has been shown that the younger the patient, the lesser the risk of partial gastrectomy and that this risk increases progressively with age, the average risk in the series being 16 per cent for all age groups. The mortality rate for gastric resection among females was somewhat less than that for gastric resection among males; it was 12.8 per cent for the females and 17.3 per cent for the males. The risk of resection was proportionate to the size of the lesion, and this was probably due to the fact that the larger the lesion, the greater the extent of stomach it was necessary to remove—hence, the more difficult the operation. Similarly, the grade of malignancy also influenced the risk of gastric resection, for the risk increased progressively as the grade of malignancy increased, being 7.5 per cent in cases of grade 1 tumor and 18.3 per cent in cases of grade 4 tumor.

An additional factor influenced the mortality rate of gastric resection. It is a factor which I have not as yet mentioned and which may have more significance than may appear on superficial examination; it is that the risk of resection among those patients in whom free hydrochloric acid was present was just half that among those who had achlorhydria, being 10 to 12 per cent in cases in which free hydrochloric acid was 30 or more degrees and 20.2 per cent in cases in which achlorhydria was present.

It might be assumed that patients with free hydrochloric acid are those who have smaller lesions which might be of the lower degrees of malignancy, but earlier in this paper I stressed the fact that such is not the case, for the percentage of small and large lesions and the percentage of lesions of low and high grade malignancy among patients with free hydrochloric acid and those with achlorhydria are about comparable.

SUMMARY

The hopeful aspect of the surgical treatment of cancer of the stomach has been that in 28.9 per cent (31.9 per cent, when the figure is adjusted for the normal death rate) of cases in which the lesions were removed

surgically, irrespective of the grade of malignancy or involvement of the regional lymph nodes, the patients were living and well five years or more after operation. If the survival curve is compared with the survival curve for the normal population, it is noted that the two curves are practically parallel for the period of more than five years beyond the survival of patients who have undergone gastric resection.

The five year survival rate after resection, computed on the basis of Broders' index of malignancy, was 86.2 per cent in cases in which the lesion was graded 1 (the differentiation ranging from 75 to 100 per cent); 58.8 per cent in cases in which the lesion was graded 2 (the differentiation ranging from 50 to 75 per cent); 30.2 per cent in cases in which the lesion was graded 3 (the differentiation ranging from 25 to 50 per cent), and 23.3 per cent in cases in which the lesion was graded 4 (the differentiation ranging from 0 to 25 per cent).

The five year survival rate and the rate of resectability among patients less than 40 years of age were surprisingly high when compared with the general average. In all age groups the rate of resectability was higher, and the operative risk was less in females than in males.

In 1.7 per cent of the cases resection was done for sarcoma.

Attention is called to the high incidence of ulcer-like dyspepsia among patients who have cancer and to the temporary effective response, measured by relief of pain, to a nonsurgical regimen in 80.6 per cent of such cases, indicating the danger in the making of a differential diagnosis between benign and malignant lesions of the stomach on the basis of symptoms alone.

Although the roentgenologist was able to demonstrate the presence of a lesion in the stomach in 98 to 99 per cent of the cases, in only 75.3 per cent was he able to designate the lesion unqualifiedly as cancer. On the other hand, it is interesting to note that a report of gastric ulcer was made by the roentgenologist concerning 10 per cent of the patients.

About 20 per cent of the patients operated on for cancer of the stomach had a free hydrochloric acid content of more than 30 degrees.

Precancerous lesions, such as chronic gastric ulcer and benign polyps, should be removed surgically.

The preferable procedure in the treatment of cancer of the stomach is partial gastrectomy by the method of Billroth; for the most part, I employed this operation as modified by the indirect anastomosis of Polya or Polya-Balfour type. Anastomosis of the Billroth I type was used successfully in a series of cases and was associated with a lower mortality rate than the Polya operation.

SUPERFICIAL SPREADING TYPE OF CARCINOMA OF THE STOMACH

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NEW YORK

Carcinoma of the stomach starts in the epithelial mucus-producing cells of the mucous membrane and grows outward from one or more focal points in all directions, i. e., into the lumen, along the gastric wall parallel to the lumen and toward the serosa. However, different tumors vary in the speed with which they grow in these various directions, and this accounts for the morphologic characteristics of the different gross types of gastric carcinoma. For instance, there is the fungating tumor, which grows chiefly into the lumen; there is the linitis plastica type, the growth of which runs parallel to the lumen in all of the gastric coats, and there are the ulcerated cancer and the cancer developing at the margin of a preexisting peptic ulcer, the growth of which is usually directed chiefly toward the serosa. In a little more than half of the resected stomachs, growth apparently occurred at comparable rates in all three directions, producing a tumor without distinguishing characteristics.

Until March 1937, the foregoing classification covered all the different gross forms of gastric carcinoma which I had observed. In that month I encountered the first of a series of tumors which displayed a different pattern of growth. In this form, growth starts in the mucosa and spreads superficially in the mucosa and the submucosa without penetrating deeply into the muscularis until it has covered a considerable surface area. In 1 instance the area involved measured 9 by 6 cm. without penetration beneath the submucosa. Cases have accumulated rapidly until now I have a collection of 15 cases of tumor of this type. In all of them the antral portion of the stomach in the vicinity of the lesser curvature was involved.

Grossly, carcinoma of this type is characterized by reddening, irregularity and slight nodular thickening of the diseased mucosa. Almost always this is associated either with a shallow bowl-shaped ulcer extending to the submucosa or with a characteristic deep-penetrating peptic

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ulcer, from the periphery of which the superficial tumor growth spreads outward in the mucosa and the submucosa. In 9 of the cases the growth started at the margin of a peptic ulcer; in 5 the cancer was ulcerated, and in 1 case there was only superficial erosion without real ulceration. Despite the fact that the tumors were superficial, it was observed, when resection was performed, that 7 of the 15 had already metastasized either to the superior or to the inferior gastric lymph nodes.

The histologic appearance of neoplasms of this type varies greatly in degree of differentiation, from the formation of atypical acini and more

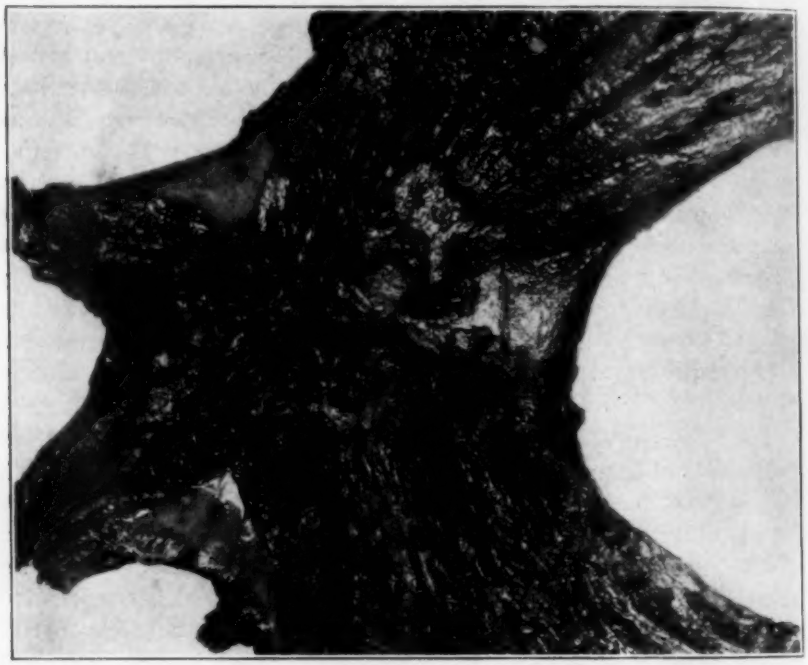

Fig. 1 (case 5).—Superficial spreading carcinoma with erosion but no true ulceration. The stomach is shown opened along the greater curvature with the hypertrophied pylorus at the left. The tumor covered an area 6 by 9 cm. on the lesser curvature and the adjacent anterior and posterior walls of the distal half of the stomach. There was patchy involvement of the mucosa and submucosa alone.

or less mucin to completely undifferentiated carcinoma with rounded cells appearing singly or in small clusters. Four of the cancers in this series involved the mucosa in a patchy fashion with areas free from neoplasm between the islands. However, the important feature common to all, whether they started from a single focus or from multiple foci, was the superficial spread. In only 5 of the 15 cases was there any invasion of the muscularis, and in these the penetrating growth was

found in only one microscopic area after examination of numerous preparations. In the majority of the cases the cancerous growth was associated with fibrous thickening of the gastric wall and hypertrophy of the muscular coat. The pyloric ring muscle was hypertrophied in 10 of the 15 cases. In all, gastritis involved the mucosa and usually the other coats as well.

The clinical problem of diagnosis was to decide whether the patient was suffering from gastritis, peptic ulcer, cancer or some combination

Fig. 2 (case 14).—Superficial ulcerated carcinoma with spread into the surrounding mucosa, covering a total area 3.2 by 3 cm. The stomach has been opened along the greater curvature with the hypertrophied pylorus at the left. The cancer involves the lesser curvature and the adjacent anterior and posterior walls near the pylorus.

of these three. Most of the patients had suffered from one to ten years with symptoms suggesting gastric or duodenal ulcer. Two thirds of them actually had peptic stomach ulcers with hypertrophy of the pyloric and antral muscles, and 14 were noted to have more or less six hour retention, probably due to muscular spasm since in none of them was

the stomach mechanically obstructed. Acid secretion was variable. Most of them had sufficient fibrosis to stiffen the gastric wall. This, together with the extension of the cancer in the mucosa, muscularis mucosae and submucosa, caused distortion of the peristaltic waves and disarrangement of the mucosal folds, sometimes with the formation of small mucosal nodules which could be visualized by roentgenograms and seen through a gastroscope.

From March 1937 to Oct. 12, 1941, 69 gastric neoplasms diagnosed as carcinomas have been resected in the Presbyterian Hospital. As 15

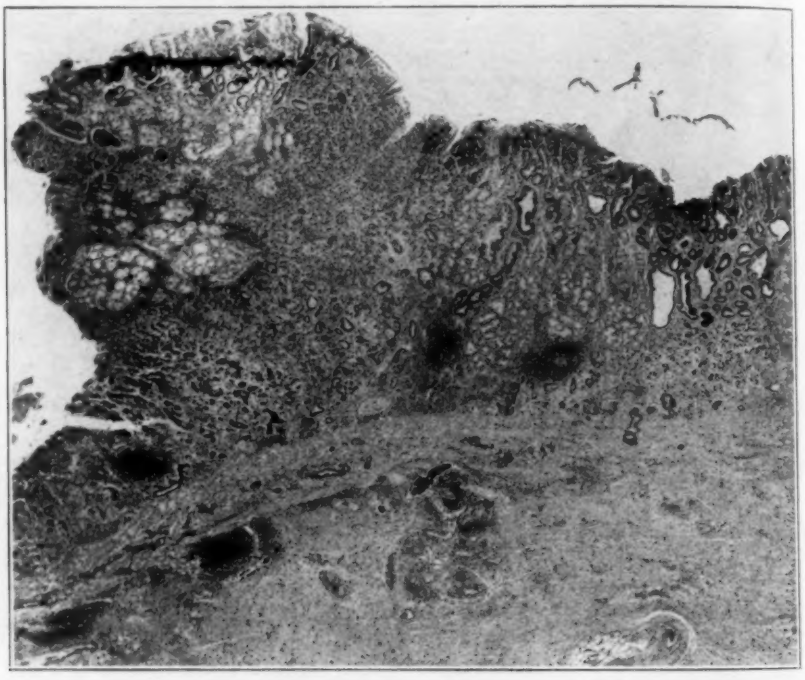

Fig. 3 (case 14).—At the left is seen the bed of the shallow ulcer shown in figure 2. The carcinoma occupying it extends through the still undestroyed mucosa to the right. It has just penetrated the muscularis mucosae and has invaded lymphatics in the superficial submucosa. Metastases were found in the superior gastric lymph nodes, but there was no deeper penetration of the wall than is shown.

of them showed the superficial spreading type of growth, this means that nearly 22 per cent were of a type never before seen among the 105 cases of carcinoma in which resection was done from 1916 through February 1937. This form of cancer of the stomach is not unknown, but its existence is appreciated by few of those concerned with diagnosis.

Cases have been reported by Mallory,[1] Ewing,[2] Konjetzny,[3] Gutmann, Bertrand and Péristiany[4] and Baker,[5] and suggested by Schindler and associates[6] but without exact description. Ewing and Mallory both expressed the belief that a majority of these cases, especially those in which the involvement is limited to the superficial part of the mucosa and in which skip areas are present, leaving free zones between, are instances of so-called cancer in situ, meaning by that carcinoma developing simultaneously in multiple foci. This hypothesis seems to me to

TABLE 1.—*Data on Fifteen Patients with Superficial Spreading Carcinoma of the Stomach*

Patient	Sex	Age, Years	Duration of Symptoms Before Operation, Mo.	Pyloric Hypertrophy	Six Hour Retention, per Cent	Acidity *		Associated Classification †	Isolated Superficial Foci	Invasion of Muscularis	Metastasis to Lymph Nodes	Time After Operation, Mo.	Result
1	F	66	12	Yes	?	.....	.....	U.C.	Yes	No	Yes	13	Died
2	M	45	84	Yes	90	38/51	98/111	C.P.U.	No	Yes	No	47	Well
3	M	51	36	No	50	.....	.....	C.P.U.	Yes	No	No	36	Well
4	M	37	8	Yes	15	0/5	10/58	C.P.U.	No	No	Yes	36	Well
5	M	50	12	Yes	50	0/20	.....	None	Yes	No	No	39	Well
6	F	61	8½	No	80	.....	.....	C.P.U.	No	No	No	33	Well
7	M	34	120	Yes	50	.....	.....	U.C.	Yes	No	No	24	Well
8	M	60	5	No	50	28/38	.....	U.C.	No	Yes	No	31	Well
9	F	54	12	No	95	.....	.....	C.P.U.	No	Yes	No	18	Well
10	M	52	4	Yes	5	22/34	65/80	U.C.‡	No	No	Yes	17	Well
11	F	55	24	Yes	60	0/89	.....	C.P.U.	No	Yes	Yes	19	Well
12	M	50	60	No	Slight	18/22	.....	C.P.U.	No	No	No	16	Well
13	F	67	12	Yes	30	25/55	.....	C.P.U.	No	No	Yes	10	Well
14	F	58	24	Yes	10	24/43	71/91	U.C.	No	No	Yes	9	Well
15	M	56	24	Yes	100	.....	0/165	C.P.U.	No	Yes	Yes	(Recent)	

* On the left, free hydrochloric acid over total acid; on the right, the same forty minutes after the injection of histamine.

† U.C., ulcerated cancer; C.P.U., cancer in a peptic ulcer.

‡ Unrelated peptic ulcer also present.

1. Cabot Case 21111, New England J. Med. **212**:481, 1935. Mallory, T. B.: ibid. **225**:87, 1941.

2. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 688; ed. 4, 1940, pp. 709-711; Am. J. Surg. **31**:204, 1936.

3. Konjetzny, G. E.: Compt. rend. IIe Cong. internat. de gastro-entérol., 1937, p. 590.

4. Gutmann, R. A.; Bertrand, I., and Péristiany, T. J.: Le cancer de l'estomac au début, Paris, Gaston Doin, 1939, pp. 92, 218 and 389-404.

5. Baker, J. W.: Northwest Med. **40**:277, 1941.

6. Schindler, R.; Steiner, P. E.; Smith, W. M., and Dailey, M. E.: Surg., Gynec. & Obst. **73**:30-39, 1941.

require further investigation before it can be accepted, but whether the growth starts from a single focus or from multiple foci, the involvement and spread remain superficial.

It has been natural to speculate as to why I should suddenly begin to note these cases in considerable numbers when they were never noted at all by me before 1937. Since in 14 of the 15 the cancer was associated with an ulcer of either a benign or a malignant type, it was decided to determine the percentage of cases of ulcerated cancer and cancer in peptic ulcer in the total number of cases of carcinoma of the stomach in which resection was done in each succeeding quinquennial period, beginning in 1916. The results are shown in table 2. There has been an almost steady increase in the percentage of cases in which carcinoma starts in, or simulates, peptic ulcer of the stomach. This seems to me to parallel

TABLE 2.—*Percentage Relation of Cases of Ulcerated Gastric Carcinoma and Carcinoma in Peptic Ulcer to Total Number of Cases of Carcinoma of the Stomach in Which Resection Was Done at the Presbyterian Hospital*

Quinquennial Period	Total Cases in Which Resection Was Done	Cases of Ulcerated Carcinoma and Carcinoma in Ulcer	
		Number	Per Cent
1916-1920	17	2	11.7
1921-1925	22	4	18.0
1926-1930	21	3	14.2
1931-1935	45	10	22.2
1936-1940	59	22	37.3

the increase of interest in patients with ulcerated lesions of the type described and the marked development of ability to recognize the condition at an earlier stage, so that earlier operations are done. Whether or not this is the sole explanation for the sudden appearance of the superficial spreading type of cancer in resected stomachs is uncertain. Two thirds of the patients suffered from gastric symptoms for more than a year preceding operation, and a like proportion of the cancers covered areas of mucosal surface in excess of 12 sq. cm. with a maximum of 54 sq. cm. Therefore it would seem that plenty of opportunity was afforded for deeper penetration if these tumors had behaved like those diagnosed as gastric carcinoma before 1937.

Whatever the explanation of the sudden appearance of the superficial spreading type of gastric carcinoma may be, the results of treatment by partial gastrectomy have been gratifying, even though not enough time has elapsed to determine the five year survival rate. All of the patients survived the operation; 1 died of cancer thirteen months after

resection. Of the 14 survivors at the time of writing, 4 have passed three years; 3 are living between two and three years; 4, between one and two years; 3, less than one year after operation. All of these survivors are symptom free.

It seems probable that concentration on the diagnosis of early cancer of the stomach, particularly in the group suffering from ulcer symptoms, will bring to light in a larger number this type of superficial spreading carcinoma, which seemingly offers a far better hope of cure by surgery than the average.

PATHOGENESIS OF CHOLECYSTITIS

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Considerable confusion exists at the present time as to the pathologic and the physiologic mechanism involved in inflammatory processes in the gallbladder. These difficulties have been reflected in the wide divergence of opinion relative to the treatment of these inflammatory processes in various stages. Efforts directed at the solution of the problem by clinical statistical methods have apparently added more to the confusion than to the clarification of opinion. The following studies are based on an attempt to approach a better understanding of the subject by experimental and clinical analysis of the pathologic factors involved.

Any explanation of the pathogenesis of cholecystitis must take account of many unique features by which cholecystitis differs from most inflammations elsewhere in the body. These features present themselves both clinically and pathologically.

In the clinical picture of cholecystitis there are many characteristics that are unusual when compared with inflammation in other organs. It is one of the inflammatory processes most frequently encountered in the abdomen. Mentzer [1] noted gross evidence of cholecystitis in 62 per cent of the gallbladders removed at necropsy in a study of 612 patients. While this incidence is perhaps unusually high in comparison with that found in some of the other studies, by reason of the nature of the clinical material available, it represents an index of the possible frequency of the disease. VonKaenel [2] studied a series of 3,000 consecutive autopsies at the St. Louis City Hospital—a general hospital—and found the incidence of gross evidence of cholecystitis to be 17.5 per cent. Thus there is considerable variation depending on the type of analysis made and the many factors involved. In some countries the lesion seems to be much less common. Again, cholecystitis is seen more frequently in persons possessing the sthenic and the hypersthenic body habitus. This

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1. Mentzer, S. H.: A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, Surg., Gynec. & Obst. **42**:782, 1926.

2. VonKaenel, J. E.: Personal communication to the authors.

is an old observation. While the exact significance of such an observation cannot be stated at present, it has been assumed to be related in a metabolic capacity.

Cholecystitis is relatively uncommon in children and in young adults (in whom bacterial inflammations are so often seen). There is a definite increase in the frequency of the disease with increasing age; it is much more prevalent in the fourth, the fifth and the sixth decades of life. It seems to bear but little association with ulcerative lesions of the intestinal tract and suppurative processes of the peritoneum, which are so often seen in younger people. If a bacterial invasion from the portal tract were the only pathogenic factor to be considered, one would expect a frequent association with such lesions. It is indeed questionable whether the triad of peptic ulcer, appendicitis and cholecystitis, stressed especially by Moynihan, is found with frequency enough to make it of any particular importance.

There is a decided preponderance of female over male patients. This fact, like that relating to body habitus, may have to do with altered metabolic processes, since these seem to be particularly concerned with the problem of cholelithiasis.

There is a definite relation between cholecystitis and cholelithiasis, despite the fact that stoneless cholecystitis is not infrequent. Seldom is cholelithiasis seen for any great length of time without pathologic changes in the wall of the gallbladder. While it is difficult to separate cause and effect in such instances, these changes sometimes differ strikingly from those produced by the presence of calculi in other organs. Stones in the gallbladder sooner or later may be concerned with either partial or complete obstruction of the cystic duct. The importance of this will be considered later.

Similarly, the pathologic picture seen in cases of cholecystitis is unique in many respects. Gangrene is not uncommonly observed with a patent cystic artery and abundant collateral circulation, both between the liver and the gallbladder and between the gallbladder wall and adjacent viscera. So profuse is the circulation between the wall of gallbladder and the liver that ligation of the cystic artery in the experimental animal produces no apparent circulatory damage. We have demonstrated this on numerous occasions. This disease therefore differs from gangrene of the common type seen in other portions of the body, in which arterial obstruction is the chief factor. It is highly suggestive of a direct action of some substance producing necrobiosis of the tissue.

Acute inflammation of the gallbladder is usually associated with gross and microscopic evidence of a preexisting chronic inflammatory process, i. e., with the fibrosis and the infiltration by cellular elements usually

associated with chronicity. It is rare to encounter an acute inflammatory process in the gallbladder in an area that has not been the seat of a preexisting inflammatory lesion.

In an area of acute cholecystitis the predominant pathologic feature is increased vascular permeability; there is also evidence of direct injury to tissue. The former presents itself chiefly as edema, extravasation of blood throughout the wall and monocytic infiltration with a relatively small amount of granulocytic invasion in proportion to the acuteness of the inflammation. The evidence of injury to tissue may be seen in definite necrotic areas, which often are irregularly distributed throughout the wall, and in fibrosis. In the early stage of the lesion these fibroblasts are young and edematous.

Acute cholecystitis unassociated with obstruction of the cystic duct is extremely rare. In an analysis of 508 cases Judd [3] found that stone was present in the cystic duct in 484 of them (95.4 per cent). In a collection of 3,863 cases, Berk [4] reported stone obstructing the cystic duct in 92.5 per cent of the cases. In the remaining small group the obstruction was usually due either to an inflammatory process or to a preexisting congenital anomaly as has been stressed by Seelig [5] and by Gage.[6]

Often a specific inflammation may be seen in which the inciting factor is a lipid. This is more commonly observed in so-called cholesterosis of the gallbladder. Mild inflammation also is a constant finding in the gallbladder wall in which there is cholesterosis. Evidence of a deposition of bile or some of its components in the gallbladder wall may occasionally be seen in cases of chronic cholecystitis, as will be illustrated in this report.

EXPERIMENTAL OBSERVATIONS

From a consideration of the aforementioned features it seems justified to conclude that any causative agent able to effect such a pathologic syndrome as that seen in cholecystitis must have the ability to produce a particular injury to tissue, must have easy access to the gallbladder and must have its action increased with obstruction of the cystic duct. There must be present likewise a potentiality of modification during certain metabolic phases.

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3. Judd, E. S., and Phillips, R.: Acute Cholecystic Disease, Ann. Surg. **98**: 771, 1933.

4. Berk, J. E.: The Management of Acute Cholecystitis, Am. J. Digest. Dis. **7**:325, 1940.

5. Seelig, M. G.; Bile Duct Anomaly as a Factor in the Pathogenesis of Cholecystitis, Surg., Gynec. & Obst. **36**:331, 1923.

6. Gage, M.: The Surgery of Acute Cholecystitis, New Orleans M. & S. J. **91**:607, 1939.

It occurred to us that bile might fulfil many of these qualifications and that it should be studied with the idea of its being a causative factor in the production or the instigation of cholecystitis. Some of these studies were recently recorded in a preliminary communication [7] which will be expanded in this report.

Effect of Bile on Tissues.—That massive extravasations of bile into the peritoneal cavity are particularly injurious has long been recognized. Elaborate studies on the mechanism involved have been made particularly by Rewbridge [8] and co-workers. This damage may or may not be associated with secondary bacterial invasion, although the latter is not uncommon, particularly in the peritoneal cavity, where the close proximity of the intestinal tract makes contamination more accessible. Again, a similarly destructive action of bile on tissues when there is a reflux of bile in the excretory ducts of the pancreas has long been observed. It is now a well established fact that when such a regurgitation takes place a series of changes occurs in the pancreatic tissue leading to tissue necrosis and hemorrhagic extravasation.

The action of bile on tissues is generally direct and apparently dependent on the concentration of the bile and on many of the different components of bile. The latter seem to be chiefly derivatives of cholic acid. When whole bile or any of these bile substances are injected into tissue, one of the earliest changes is a marked increase in vascular permeability as evidenced by edema. The transudation of plasma is often rapid and extensive and may be associated with diapedesis of red blood cells. Where the concentration of bile is greatest, actual necrosis quickly occurs. Granulocytic reaction is relatively slight, and most of the leukocytes present are of the monocytic series. One of the outstanding features is excessive and early fibroblastic proliferation. This is first seen at the periphery of the lesion, where the concentration of bile has not been so great. Such fibroblastic proliferation is in keeping with tissue reaction to steroids in general. Figure 1 illustrates some of the changes described.

Attention may be drawn to the fact that the reaction described is identical with that seen in different phases of clinical cholecystitis, namely, gangrene, edema, ecchymosis, round cell infiltration and fibrosis, depending on the severity of the involvement and the length of time the process has existed. These reactions likewise are subject to change by secondary bacterial invasion.

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7. Womack, N. A., and Bricker, E. M.: Pathological Changes in the Gallbladder Wall Due to the Action of Bile, Proc. Soc. Exper. Biol. & Med. **45**:710, 1940.

8. Rewbridge, A. G.: The Etiologic Role of Gas-Forming Bacilli in Experimental Bile Peritonitis, Surg., Gynec. & Obst. **52**:205, 1931.

Effect of Obstruction of the Cystic Duct.—We have previously referred to the frequency of the association of complete obstruction of the cystic duct with acute forms of cholecystitis. Since the two situations are almost universally found together, experiments were carried out to determine the importance of this relation.

(*a*) In 8 dogs, a curved cannula was inserted into the cystic duct and the bile aspirated from the gallbladder. The gallbladder was gently flushed with physiologic solution of sodium chloride, and an amount of this solution equivalent to the amount of bile withdrawn was left in the gallbladder. The cystic duct was ligated

Fig. 1.—Subcutaneous tissue of a dog two weeks after an injection of normal dog bile, showing the toxic effect of bile on tissue.

with fine silk at the point of injection. The animals were killed at different periods from one week to four months after operation. In 7 instances, the gallbladder was distended with mucus, and the wall was thin with no evidence of inflammation (fig. 2). In the other instance there was a purulent exudate in the lumen of the gallbladder, and the gallbladder wall showed evidence of acute inflammation. It would seem, therefore, that complete occlusion of the cystic duct without the presence of bile in the gallbladder results in distention with mucus unless it is associated with severe bacterial infection. In cases in which this is present, true empyema may supervene.

(*b*) The effect of complete obstruction of the cystic duct with the gallbladder bile left intact was next studied. Six dogs were used. There was slight variation in the results. Those dogs killed in the first few weeks showed a definite mild

subacute reaction. Those animals killed at the end of four months showed distention with mucus secretion and only slight fibrosis in the gallbladder wall. It was apparent that complete imprisonment of normal gallbladder bile in the dog was associated with moderate inflammatory change from which the organ could probably recover. It is well to bear in mind that in all probability the type of

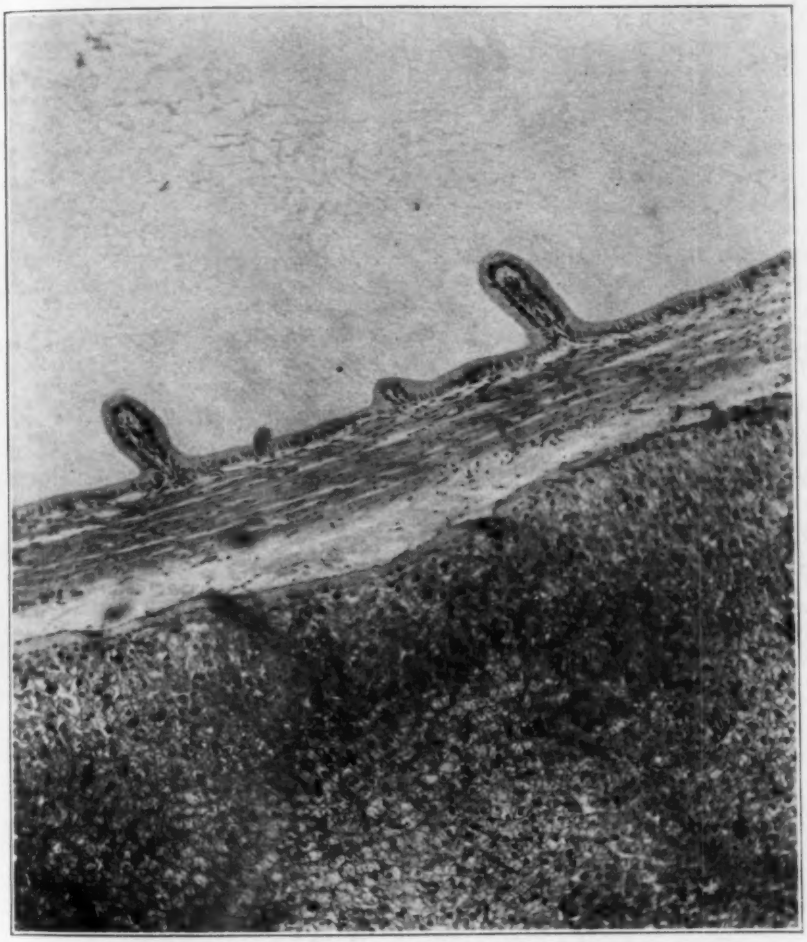

Fig. 2.—Gallbladder of a dog sixteen weeks after ligation of the cystic duct with replacement of the gallbladder bile by physiologic solution of sodium chloride. There is no demonstrable lesion in the gallbladder or the adjacent liver tissue.

reaction seen after such an experiment will vary in different animals according to the concentrating ability of the epithelium of the gallbladder and the nature of the bile peculiar to that species. In man many of the substances that we have found to be irritating to tissue are found in relatively high concentration, and furthermore the concentrating power of the gallbladder is excellent.

It is therefore probable that the tissue reaction described will be much more marked after cystic obstruction in the human being with bile of ordinary concentration.

(*c*) Because of the difference in the bile salt and the cholesterol content of dog's bile in comparison with human bile, studies were next carried out on the effect of imprisonment of concentrated dog's bile. Dog's gallbladder bile was concentrated to half its normal volume by extraction of its water at room temperature. After rapid evaporation, sterilization was assured by heating the bile for thirty minutes in a water bath; after this the bile was sterile on culture. There is no available evidence that heating at such a temperature produces any appreciable change in the chemical nature of the bile. Eleven dogs were used in the experiment. In 10 of them, a cannula was inserted in the cystic duct and the bile aspirated from the gallbladder. Concentrated bile prepared as described was reinjected into the gallbladder in an amount not quite equivalent to that withdrawn. The cannula was removed and the cystic duct ligated at the point of injection. In the remaining animal a fine needle was inserted in the fundus of the gallbladder, and through this the normal bile was aspirated and replaced with concentrated bile. The cystic duct was not disturbed.

The dog in which the cystic duct was not obstructed was killed at the end of two weeks. Both grossly and microscopically the gallbladder appeared normal (fig. 3*A*).

The remaining 10 dogs were killed at periods varying from twenty-four hours to four months. Those dogs killed in the first two days were killed at a time when they were obviously moribund. These animals all presented the same lesion, namely, one of gangrene of the gallbladder with severe hepatic injury but no evidence of peritonitis except a local adhesive type in the region of the gallbladder. The wall of the gallbladder was thickened owing to edema and hemorrhage in the wall and under the serosa. There was considerable necrosis with a minimal amount of polymorphonuclear infiltration. That portion of the liver adjacent to the gallbladder showed a similar change (fig. 3*B*). The picture in no way differed from that seen in acute cholecystitis in the human being. Vomiting, fever and leukocytosis were all present in the experimental animals.

Other animals apparently were able to withstand the damage produced and were killed at a later date (fig. 3*C*). They all showed the characteristic picture of chronic cholecystitis. In some animals in which this type of lesion was found the cystic duct was seen again to be patent. In 2 instances the lesions produced were much less marked. In 1 of these there was a mucocele, and in the other there was a precipitation of the bile solids in the form of many small soft stones. Whether the outpouring of mucus or the precipitation of stones represents a protective mechanism cannot be stated.

(*d*) To determine whether or not this bile action was nonspecific so far as species was concerned, the experiments were repeated with a solution of commercial dried bile.[9] Distilled water was added to the powdered dried bile until the concentration was double that of normal gallbladder bile. Sterilization was obtained by placing the solution in a water bath for thirty minutes and was checked by culture.

The technic described in section *c* was now carried out. In 9 dogs, the bile was aspirated through the cystic duct, the dried bile solution reinjected and the

9. The solution of commercial dried bile (Desicol) for these experiments was supplied to us by the manufacturer, Parke, Davis & Co.

cystic duct ligated. In 3 dogs the gallbladder was aspirated through the fundus and the solution of commercial dried bile reinjected without manipulation or obstruction of the cystic duct.

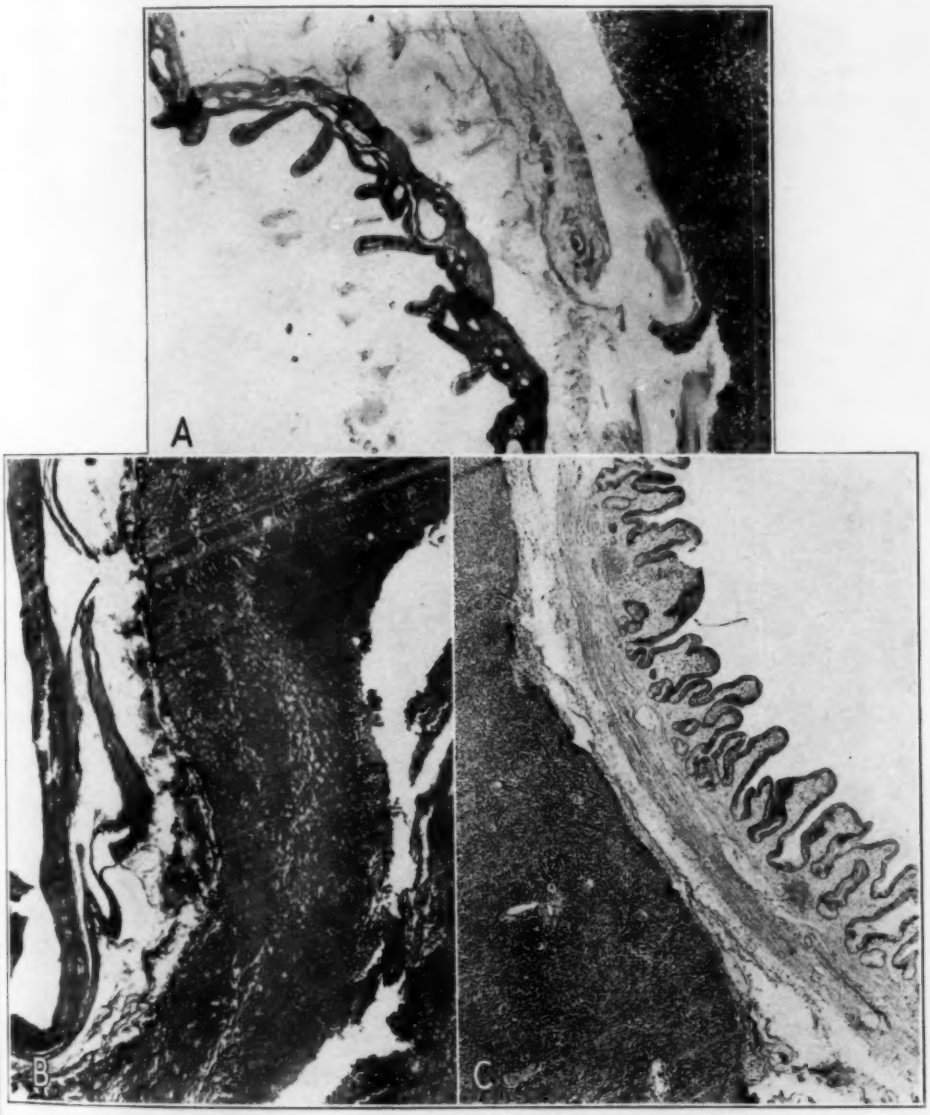

Fig. 3.—The effect of dog's bile concentrated one time on the gallbladder wall: *A*, in a dog without obstruction of the cyst duct. Note the normal appearance one week later. *B*, in a dog with obstruction of the cystic duct. Note necrosis extending into the liver one week later. *C*, in a dog with obstruction of the cystic duct. One week later the reaction was not so severe as that shown in *B*.

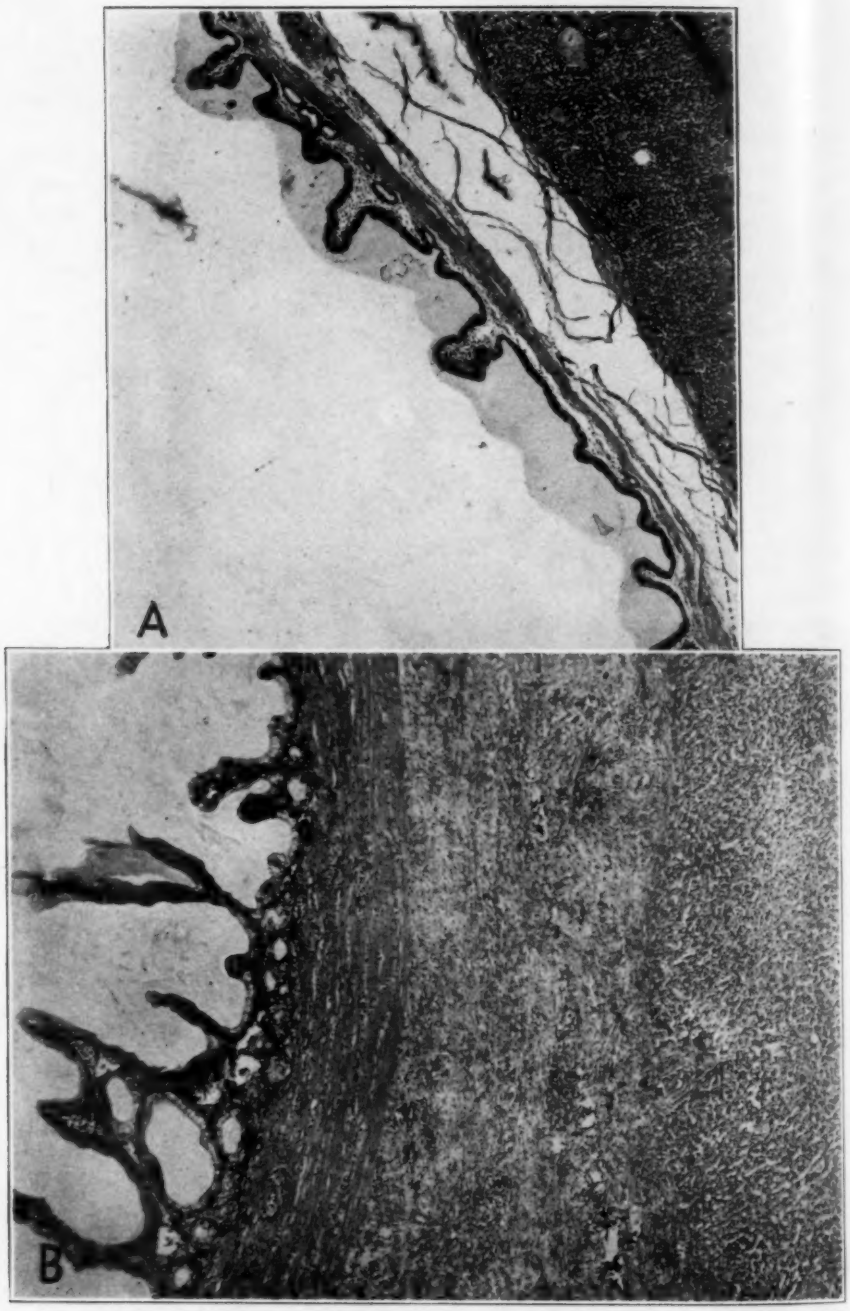

Fig. 4.—In this figure and in figure 5 the effect on the gallbladder of a solution of dried hog bile approximately equivalent to gallbladder bile concentrated one time: *A*, in a dog without obstruction of the cystic duct, one week after injection. Note normal gallbladder wall. *B*, in a dog with obstruction of the cystic duct, one week after injection.

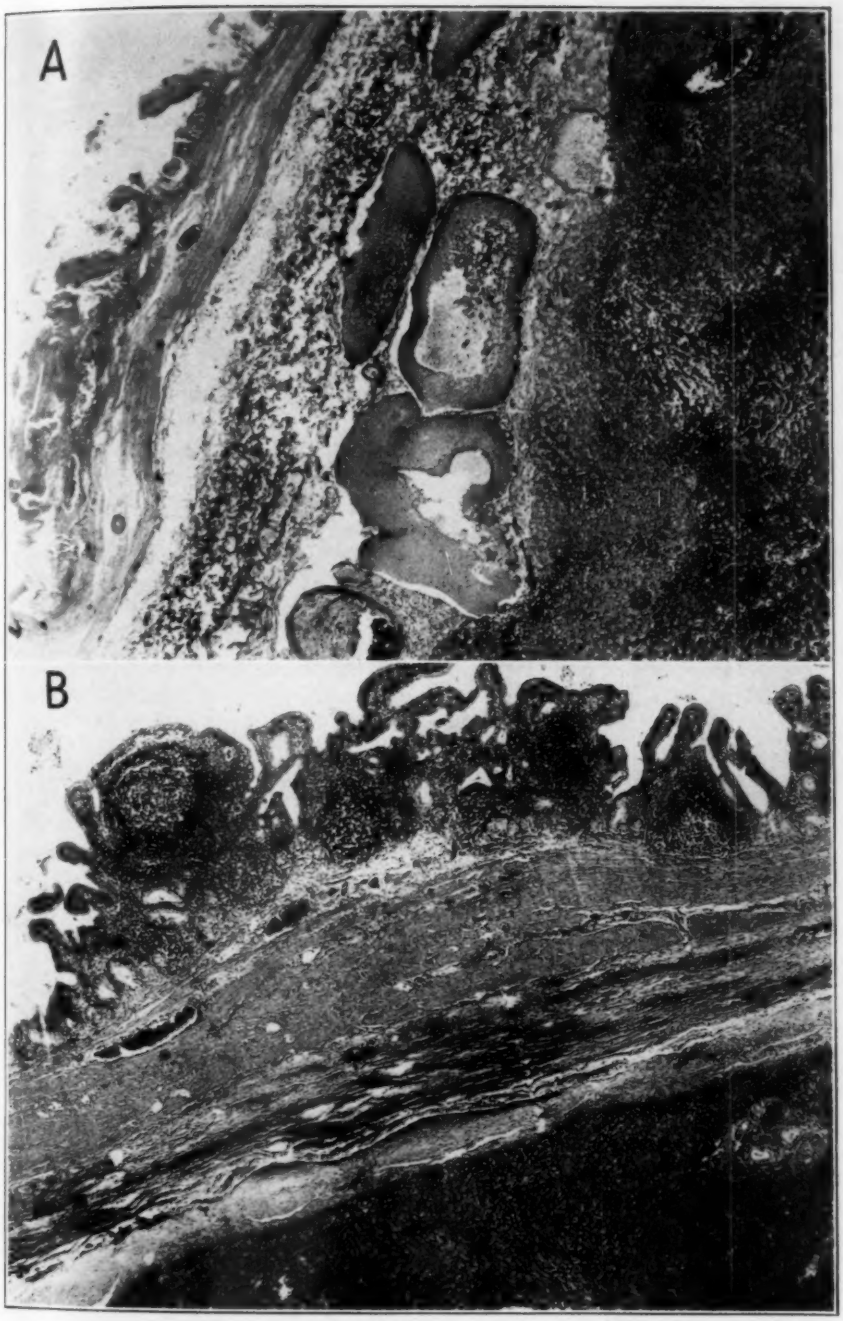

Fig. 5.—*A*, twenty-four hours after obstruction of the cystic duct. Note extensive gangrene with marked vascular dilatation. *B*, four weeks after obstruction of the cystic duct. Note the characteristic picture of chronic cholecystitis.

The animals were killed at intervals of twenty-four hours to five weeks. As we anticipated, the results were identical with those obtained when the dogs' bile was used in approximately the same concentration (figs. 4 and 5).

(*e*) We were now interested in establishing whether any particular component of bile is concerned with the production of this tissue damage. Evidence previously referred to already pointed to the fact that many of the bile steroids were capable of setting up just such an inflammatory reaction. In view of the fact that the composition of bile often differs somewhat in different species it was thought worth while to determine whether a similar change could be observed in relation to the gallbladder.

Because of the frequency with which cholesterosis of the gallbladder has been observed with the demonstration of cholesterol in the gallbladder wall, this substance was investigated first. Its well known action as a tissue irritant when present in such lesions as atheromatous plaques also was suggestive.

Accordingly, in 4 dogs, the bile was aspirated from the gallbladder through the cystic duct and replaced with an equal amount of cholesterol emulsion (1.3 per cent) in water. The cystic duct was ligated. Three other dogs were treated in a similar way; for these 2.6 per cent emulsion was used. Finally, in 8 dogs, the bile was aspirated from the gallbladder and used as a solvent for cholesterol crystals; the solution was then placed in the gallbladder through the cystic duct. Dog's bile usually contains only a relatively small amount of cholesterol, and as a result such solutions were easily prepared. Concentrations of cholesterol in bile varying from 1.5 to 5 per cent were used.

The animals were killed at intervals similar to those described in the previous experiments. The type of lesion found was generally speaking directly related to the concentration of the cholesterol. In cases in which concentrations over 3 per cent were used, necrosis of the gallbladder was frequent. In cases in which weaker concentrations were used, the picture of chronic cholecystitis was often observed to be in no way different from that in the human being. In cases in which the higher concentration was used, it was not unusual to observe degenerative changes in the liver, particularly notable around the periductal lymphatics.

Sodium desoxycholate and sodium glycocholate also were used. In a 3.5 per cent solution, the former produced such widespread necrosis that it did not lend itself well to experimentation. Often, particularly in rabbits, it was impossible to locate the gallbladder several days after the imprisonment of this substance. Conversely, sodium glycocholate was found to be the mildest of the substances used. Its effect, however, ran parallel to its concentration as did that of cholesterol.

Bacteriologic studies made in the course of these experiments have not been complete enough to warrant forming a definite opinion. Because the normal dog gallbladder and the liver so frequently show organisms, positive cultures were difficult to interpret. It is of interest to note that in 2 instances in which complete gangrene of the gallbladder was produced in a rabbit with deoxycholic acid, both aerobic and anaerobic cultures of the necrotic gallbladder wall were sterile.

Pathologic Evidence of Bile or Its Constituents in the Wall of the Gallbladder of Patients with Cholecystitis.—(*a*) Cholesterosis. This condition was recognized many years ago by Moynihan and given the name "strawberry gallbladder" by MacCarty, but its exact nature was

clearly shown by Boyd.[10] He was able to demonstrate by chemical analysis as well as by specific staining methods that the mucosal and submucosal deposits, seen grossly as yellowish white spots, were either cholesterol or cholesterol esters. He was able to demonstrate chemically many times the normal amount of cholesterol in the gallbladder. He also noted that whenever the lipid was found in the gallbladder, it was always associated with evidence of chronic inflammation. Boyd did not care to express his opinion as to whether the inflammation was the

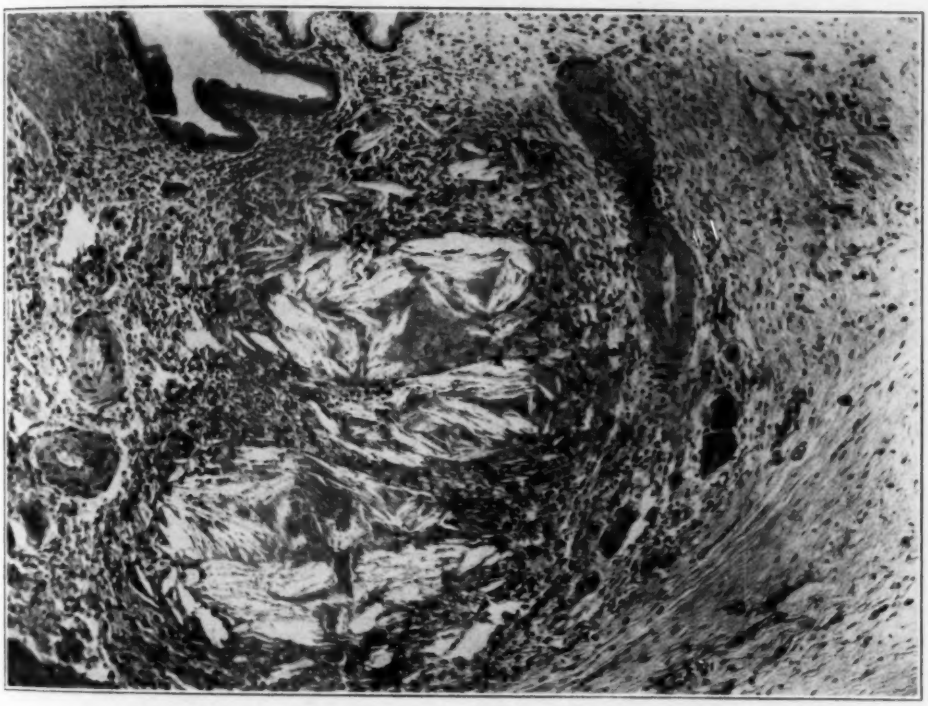

Fig. 6.—Cholesterol crystals in the wall of a human gallbladder.

cause or the effect. Sometimes when cholesterol esters are found in only slight amounts within histiocytes there may be a mild inflammatory reaction. At other times crystals of cholesterol may be found precipitated within the wall of the gallbladder as in figure 6. Whenever such a situation arises, there is generally a considerable amount of reaction, and often giant cells are found. In our opinion cholesterosis often represents an early phase of cholecystitis. While it can occur without the

10. Boyd, W.: Surgical Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1934.

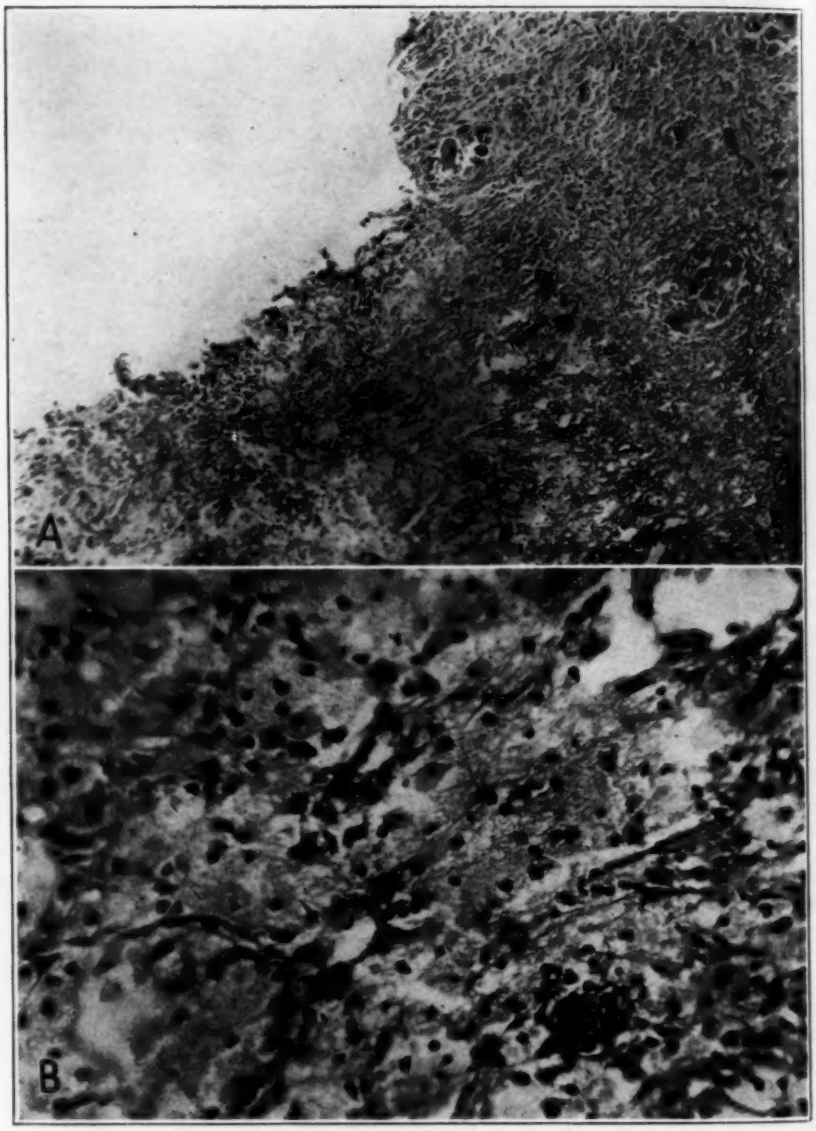

Fig. 7.—Histiocytes full of lipid in the wall of a human gallbladder, producing the picture of xanthomatosis: *A*, low power view; *B*, high power view.

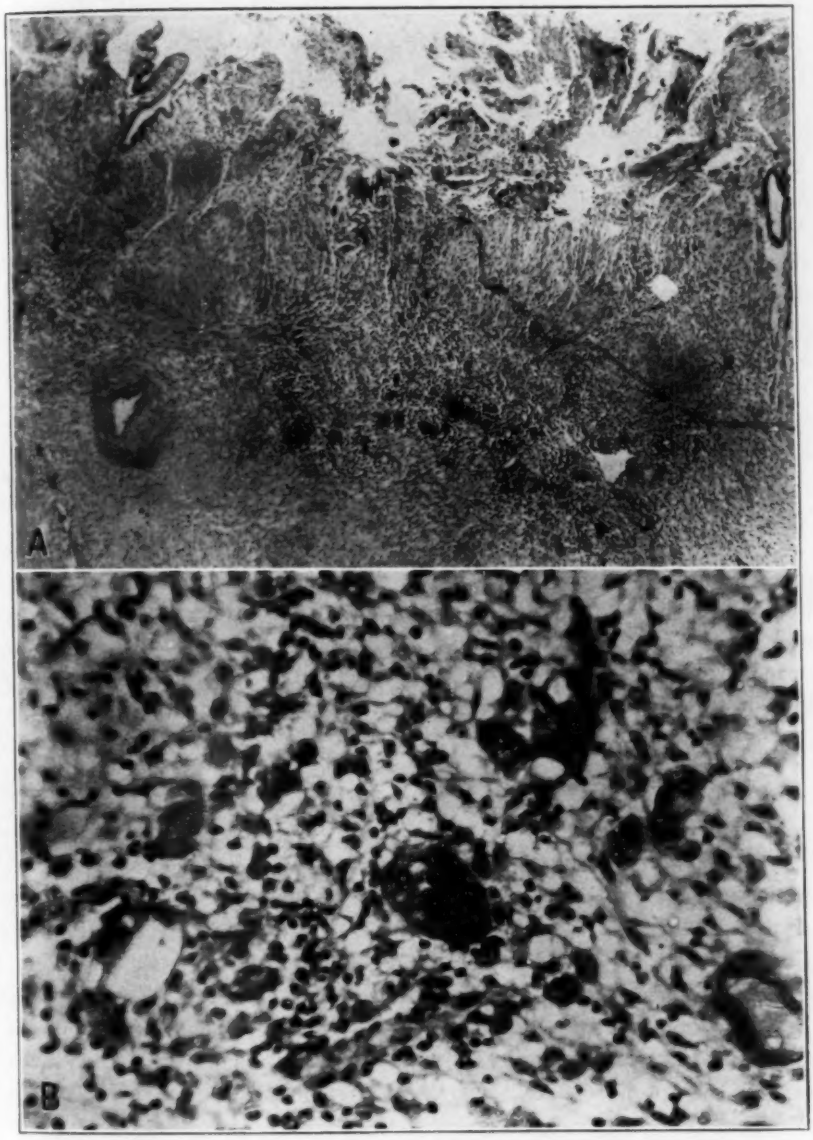

Fig. 8.—Inspissated bile in the wall of a human gallbladder: *A*, low power view; *B*, high power view. Note the type of cellular reaction and the edema present.

presence of stone, it is most frequently seen associated with cholesterol stones. Because its chemical nature can be identified, it probably represents the purest form of chemical cholecystitis seen in the human being.

(*b*) Xanthomatosis of the Wall of the Gallbladder: This is a lesion not often encountered. However, the demonstration of its presence at any time, it seems to us, is of considerable importance, for it is evidence of the fact that steroids, presumably from the bile, are found in the gallbladder wall and when present set up inflammatory reaction similar to that seen in cases of xanthomatosis elsewhere in the body. Figure 7 represents such a condition. It is interesting to notice that the epithelium of the gallbladder is completely destroyed in this area and that the wall of the gallbladder is infiltrated by histiocytes, the cytoplasm of which is swollen owing to ingested lipid. Here and there one sees islands in which there has been cellular breakdown with an associated giant cell reaction. It is possible that the lipid present in these cells is for the most part cholesterol in origin, but this we could not determine. It is important to stress the fact that the type of cellular reaction present here cannot, so far as we know, be produced by bacteria or by any form of irritant other than a lipid.

(*c*) Bile in the Wall of the Gallbladder: Much more frequently than is generally recognized it is possible to demonstrate what is apparently precipitated bile in the wall of the gallbladder. Since we have become interested in this question, we have been able to identify such a substance in many instances in which the gallbladder wall has been studied in cases of acute or subacute cholecystitis. Figure 8 represents a low and a high power view of such a situation. The dark opaque substances appear as a brilliantly yellow pigmented structure and differ in no way from inspissated bile seen in tissues elsewhere in the body. There is no evident crystallization, and the substance appears amorphous. It is interesting to note that the gallbladder shows a considerable loss of epithelium and that around the deposition of bile there is edema which is fairly well localized in some areas. There is likewise a cellular reaction, consisting of giant cells, histiocytes and lymphocytes. Early fibroblastic proliferation is also present. With the exception of cholesterosis, these types of chemical cholecystitis have been relatively rare in human beings. They were all associated with obstruction of the cystic duct, and all presented relatively marked inflammatory change of the gallbladder wall.

COMMENT

In considering the relation between these data and the causation of clinical cholecystitis, three factors may be considered to be of great importance: (1) obstruction of the cystic duct, either permanent or temporary, (2) the local damaging effect of imprisoned bile as a result

of either greater concentration or a difference in the bile constituents and (3) bacterial invasion, which generally is superimposed on injured tissue.

In our experiments, for the most part, we dealt with complete obstruction of the cystic duct. In many instances, however, in which an experiment was carried on for several months, it was found that the ligature had cut through the duct and that the lumen was again patent, allowing an ingress of hepatic bile into the gallbladder. The injury to the gallbladder wall, however, had already taken place. That complete obstruction of the cystic duct in the human being is frequently associated with inflammation of the gallbladder, which is often acute, has already been considered. That incomplete obstruction of the cystic duct will result in a less severe inflammatory reaction has recently been demonstrated by Cole and associates [11] in a convincing manner. By the production of partial occlusion of the cystic duct in dogs they found that after a number of months almost universally there were changes in the gallbladder wall identical with those seen in human beings with cholecystitis of a chronic sort. They were also able to show similar changes in the human gallbladder removed at operation in which developmental or anatomic defects were present interfering with the proper emptying of the concentrated gallbladder bile.

It is true that occasionally in cases of obstruction of the common duct due to cancer of the head of the pancreas or in the region of the ampulla of Vater, the gallbladder will be found to be greatly distended and appear to have a wall of relatively normal thickness. Actually, this is not so frequent as is generally assumed; the thinness of the wall is only apparent because of the distention. Microscopic studies of the gallbladder wall in such instances often show definite evidence of disease. When this is not present, it can easily be explained on the well demonstrated fact that on complete occlusion of the common duct secretion of bile from the liver ceases very quickly. This in turn leads to a lack of concentration of the bile due to several factors, the most important of which is the diluting action of the mucus and serum secreted by the gallbladder and the bile duct epithelium. We have frequently noticed that the secretion of mucus by the gallbladder epithelium acts to lessen the intensity of the inflammatory response to imprisoned concentrated bile in the gallbladder of the dog.

Perhaps the most common cause of obstruction of the cystic duct in the human being is cholelithiasis. Long-standing cholelithiasis is so universally associated with disease of the gallbladder wall that to find

11. Cole, W. H., and Rossiter, L. J.: The Relationship of Lesions of the Cystic Duct to Gallbladder Disease, Am. J. Digest. Dis. **5**:576, 1938. Cole, W. H.; Hughes, E. O., and Novak, M. V.: The Relationship of Lesions of the Cystic Duct to the Pathogenesis of Cholecystitis, Tr. Am. S. A., 1941, to be published.

a normal structure present is considered exceptional. Because of the difficulty of separating cause from effect, it is often impossible to evaluate accurately the part played by stone in the production of the lesion in an individual case. There are times, however, when the clinical evidence is suggestive. We have, for instance, observed soft pigment stones in the gallbladder of a child on whom splenectomy was performed for severe hemolytic jaundice of the familial type. There was moderate obstruction of the cystic duct due to precipitation within the folds, and the gallbladder wall presented the characteristic changes of well marked chronic cholecystitis. In those instances of cholesterosis with stone in which the gallbladder functions well with respect to the concentration of bile, gradual deterioration of this function can often be observed by the use of cholecystography. Instances likewise are encountered in which the classic clinical picture of biliary colic is found associated with normally concentrated bile. With the passage of time the gallbladder fails to be visualized by cholecystography, and at operation a diseased gallbladder wall is found with a minute stone imprisoned in one of the folds of the cystic duct.

No effort will be made here to consider those presumptive obstructions that appear to be due to failure of coordination of the neuromuscular mechanisms of the gallbladder and the bile ducts, which have been grouped under the term "dyskinesia." While the idea has been advanced that such lack of coordination might be the instigating factor in gallbladder disease, the evidence at the present time is not complete.

It seems apparent that interference with the ability of the gallbladder to empty itself adequately is concerned with the production of cholecystitis. Yet obstruction alone is not sufficient. As we have demonstrated, obstruction of an innocuous substance, such as physiologic solution of sodium chloride, does not result in inflammation. If an inflammatory change is to be produced, it is necessary that the obstructed substance be able to cause cellular damage. In our experiments we were able to demonstrate that bile was capable of doing this. Moreover the type of inflammation produced was in direct relation to the nature of the bile obstructed. It is well to bear in mind that the composition of bile is not constant. The type of bile salts present will often depend on the function of the liver, both as to its power of secretion and as to its power of detoxification. The latter function is related to the conjugation of bile salts with aminoacetic acid and taurine (aminoethylsulfonic acid). It is a clinical observation that frequently this function is seriously interfered with and that at such times the bile secreted may be much more injurious to tissue. We have seen several instances of acute noncalculous cholecystitis and cholangitis in which this apparently was the case. The bile factor therefore becomes a variable dependent on the composition and the concentration of the bile,

and the situation may and undoubtedly does exist in which it produces damage when there is no obstruction. In this connection it is of value to refer to one of the many brilliant experiments of Andrews and co-workers.[12] They were able to demonstrate that the injection of bile salts into the gallbladder results in acute inflammation even when there is no obstruction of the cystic duct.

It is possible that in instances of cholecystitis without apparent obstruction of the cystic duct local injury may also have been instigated by other substances than bile, for example, a reflux of pancreatic juice. This has been suggested by Wolfer[13] and by Bisgard,[14] both of whom presented evidence that pancreatic juice introduced into the gallbladder can produce serious destructive changes as it does in other tissues when it is activated.

The third factor to be considered in the production of cholecystitis is that of infection. The evidence that there is actual bacterial invasion in many cases of cholecystitis has been so incontrovertible that any other explanation of the pathogenesis has been considered unlikely by many. As we have stated earlier, however, there are many clinical and pathologic features about cholecystitis incompatible with such a simple interpretation. These features are provided for by the inclusion of the obstructive and the chemical effects already discussed. This is by no means meant to exclude the action of bacteria. Such an effect is complementary and necessary to explain the entire picture.

Considerable attention has been focused on the fact that in cases of cholecystitis bacteria are often found in the gallbladder wall and less frequently in the contents of the gallbladder. Much less attention has been given to the fact that often no organisms are found. Actually this is true in a considerable group of cases. In approximately two thirds of the cases, the gallbladder bile is sterile, while in about one third the wall of the gallbladder is sterile. The significance of this fact was not appreciated until similar studies were made on the number and the type of bacteria found in the wall and the bile of the normal human gallbladder.

In a recent communication, Andrews and Henry[15] were able to demonstrate that both quantitatively and qualitatively there was but little difference in the cultures of gallbladders of all types, including those with acute inflammation and those that were microscopically normal. In many instances of acute cholecystitis they encountered a

12. Aronsohn, H. G., and Andrews, E.: Experimental Cholecystitis, Surg., Gynec. & Obst. **66**:748, 1938.

13. Wolfer, J. A.: The Role of the Pancreatic Juice in the Production of Gallbladder Disease, Surg., Gynec. & Obst. **53**:443, 1931.

14. Bisgard, J. D., and Baker, C. P.: Studies Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, Tr. Am. S. A. **58**:572, 1940.

15. Andrews, E., and Henry, L. D.: Bacteriology of Normal and Diseased Gallbladders, Arch. Int. Med. **56**:1171 (Dec.) 1935.

gallbladder the wall and the contents of which were both sterile. We have had a similar experience. The facts, then, that an acute inflammatory process can be present in a gallbladder sterile to culture and that a rich flora can be obtained from a normal gallbladder make one hesitate to place too much emphasis on the conception of cholecystitis as simply and purely a bacterial infection.

Several years ago in a series of contributions Graham and co-workers presented evidence to prove that cholecystitis could be produced by bacterial invasion and that this invasion was probably lymphogenous in type and certainly associated closely with a similar process in the hepatic periductal areas, particularly those in the neighborhood of the gallbladder. In one of their contributions [16] they called attention to the fact that if the gallbladder wall is injured, bacterial infection is much easier to produce. It is this factor of injury, however slight, that so often initiates infection. Subsequently, the infectious process may be so severe that the factor of injury is overlooked. It is none the less important. This is a rule with few exceptions wherever infection may occur in the human body. In cases of cholecystitis the way in which such injury may occur is, as we have shown, inherent in the biliary mechanism. If the frequency of the presence of bacteria in the normal liver and the gallbladder be kept in mind, the origin of the infectious picture in cases of cholecystitis becomes apparent. Bacteria are not necessary as a factor in the production of the condition, but rather they are to be regarded as a complication in the history of the lesion that may be of great importance.

SUMMARY AND CONCLUSIONS

Experimental evidence is presented to demonstrate that in dogs complete obstruction of the cystic duct does not produce inflammation of the gallbladder wall if the imprisoned bile is replaced with physiologic solution of sodium chloride.

Complete obstruction of the cystic duct by which bile is left imprisoned in the gallbladder results in inflammation the severity and type of which are in direct proportion to the content and the concentration of the bile obstructed. This inflammation is identical with that encountered in clinical cholecystitis. Evidence is submitted to show that this inflammation is produced by the direct action of bile on tissue and that bile and its components can be demonstrated at times in the wall of the gallbladder in cases of human cholecystitis.

Bacterial infection may or may not be present. While bacterial infection may at times be of great clinical importance, from the standpoint of pathogenesis it should be considered as a complication that results when contaminated tissue is injured.

16. Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Arch. Surg. **4**:23 (Jan.) 1922.

GANGRENE AND PERFORATION OF THE WALL OF THE GALLBLADDER

A SEQUELA OF ACUTE CHOLECYSTITIS

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Almost a century ago (1844), James Duncan,[1] surgeon at the Royal Infirmary in Edinburgh, reported an instance of gangrene of the gallbladder which had ruptured, producing peritonitis, followed by death. The diagnosis was made at autopsy. In 1933, Dr. Samuel A. Vest Jr.,[2] of Baltimore, collected the reported cases of gangrenous cholecystitis; a total of 71 were gleaned from the literature, and 9 were reported as new. Twenty-three of the 80 patients died as a result of the condition—a mortality rate of 37 per cent. Gangrene of a portion of the entire wall of the gallbladder is, we believe, a sequela of acute cholecystitis and frequently leads to perforation.

By "gangrene of the wall of the gallbladder" we refer to complete necrosis of a portion of the wall in one or more areas; we do not use the term to indicate gangrene of the entire gallbladder. Our reason for this is based on the frequent observation that a single area of gangrene of the wall of the gallbladder results in perforation, as may gangrene of the entire organ. Perforation of the gallbladder is usually followed by grave complications and sometimes death. The high incidence of gangrene in patients who have acute cholecystitis has led us to record our observations of a group of patients who at operation were found to have gangrene of the wall of the gallbladder. Because one of the serious complications is perforation, we have reviewed our material carefully in search of the mechanism involved in this process.

The mechanism whereby perforation takes place in acute cholecystitis is of interest not only to the pathologist but to the surgeon and the physician. Gangrene of the wall of the gallbladder is often the result

From the Department of Surgery of the New York Hospital and Cornell University Medical College.

1. Duncan, J.: Femoral Hernia: Gangrene of the Gall Bladder; Extravasation of Bile; Peritonitis; Death, North. J. Med. **2**:151-153, 1844-1845.

2. Vest, S. A., Jr.: Gangrene of the Gallbladder, Internat. S. Digest **15**:131-160, 1933.

of changes that take place in the organ during an attack of acute cholecystitis. The findings most frequently encountered at operation are a stone impacted in the ampulla of the gallbladder, edema of the wall thus encroached on, blockage of the lymphatics, obstruction to the venous return by direct pressure on the vessel or by thrombosis and in some instances arterial occlusion. Probably no one process accounts for all perforations. For this reason we wish to call attention to another mechanism which we believe accounts for a fair proportion of perforations of the gallbladder. We consider that this process is closely associated with circulatory changes and infection, which play an important role.

The gallbladder resembles the intestinal tract in that as an organ it is a hollow viscus lined with mucous membrane supported on a wall

TABLE 1.—*The Incidence of Rokitansky-Aschoff Sinuses in Cases of Acute Gangrenous Cholecystitis*

Gangrene of the wall of the gallbladder	50
Number containing Rokitansky-Aschoff sinuses	30
Mucosa completely destroyed	15
No Rokitansky-Aschoff sinuses seen	14
Gangrene of the wall of the gallbladder with perforation	22
Number containing Rokitansky-Aschoff sinuses	15
Mucosa completely destroyed	3
No sections taken	1
No Rokitansky-Aschoff sinuses seen	3
Gangrene of the wall of the gallbladder with free perforation	3
Mucosa completely destroyed	2
Rokitansky-Aschoff sinuses seen	1

of submucosa and muscle and incompletely covered by peritoneum. Defects in the supportive structure of the intestinal tract in the presence of increased pressure within the viscus may result in protrusion of the mucosa through the defects in the wall. Examples are found in diverticula of the esophagus, duodenum and large bowel. The part played by the physical force of increased pressure within a viscus and diminished resistance in the structure of the wall is best seen in the large bowel of the aged patient with multiple diverticula. A similar process, we believe, takes place in the gallbladder. The early manifestations of diverticula of the wall of the gallbladder were recognized by Rokitansky,[3] who first described those diverticula and compared them with diverticula in the gastrointestinal tract. Aschoff[4] also considered these

3. von Rokitansky, C.: A Manual of Pathological Anatomy, translated by E. Sieveking, Philadelphia, Blanchard & Lea, 1855, vol. 2, p. 130.

4. Aschoff, L.: Bemerkungen zur pathologischen Anatomie der Cholelithiasis und Cholecystitis, Verhandl. d. deutsch. path. Gesellsch. **9**:41-48, 1905.

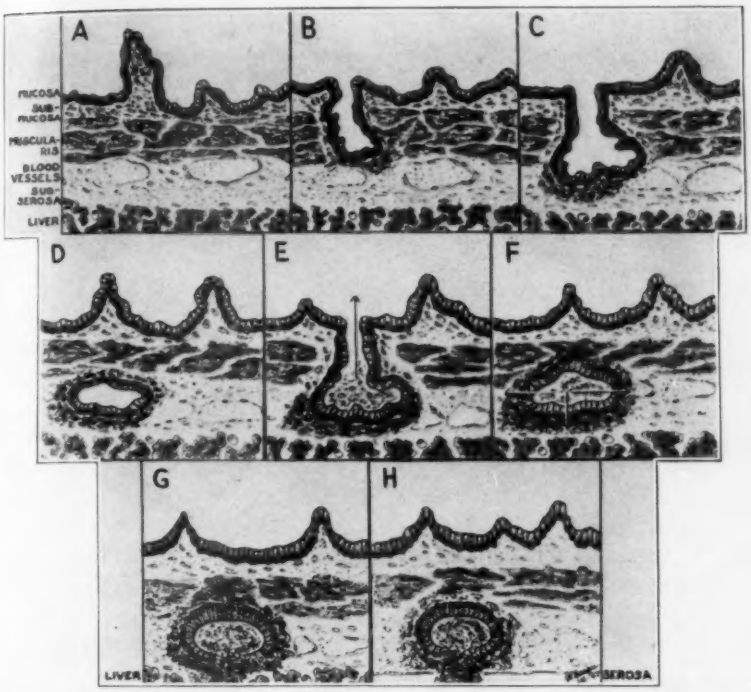

Fig. 1.—The wall of the normal gallbladder includes a mucosa of columnar epithelium on a muscular layer rich in elastic fibers supported by a strong tunica muscularis formed chiefly of bundles which have a circular direction (*A*). Where the gallbladder is covered by peritoneum, there is also a serous coat.

Throughout the gallbladder wall there are folds of mucous membrane that form crypts which are variable and often of considerable depth. When these crypts or sinuses completely penetrate the muscularis as described by Rokitansky and later by Aschoff, they are designated Rokitansky-Aschoff sinuses (*B*). With increased intracystic pressure and diminished resistance in the wall, this crypt may become branched to form a diverticulum and extend beneath the muscularis (*C*). On section such a diverticulum may appear to have no communication with the lumen of the gallbladder owing to the extension beneath the muscularis (*D*). However, if several sections are made, the communication may be traced. In a diverticulum of this type an abscess may form. If the abscess increases, it may empty either through its original channel into the gallbladder (*E*), or it may extend in the line of least resistance within the wall of the gallbladder (*F*).

Such an abscess may rupture into the liver (*G*).

An abscess in that portion of the gallbladder which is covered by peritoneum may rupture into the peritoneal cavity (*H*).

The mechanism is probably much more complicated than is shown in this schematic presentation. It is likely that impaired circulation in the presence of infection may result in numerous perforations within a comparatively small area of the gallbladder wall. We believe that rupture into the liver substance occurs frequently, while perforation into the serosa and the free peritoneal cavity is rare.

diverticula in the same light. Sinuses are frequently present in the walls of infected gallbladders. It is believed that these sinuses are enlarged and increased by forceful contractions of the organ and that in one or more the mucosal layer is forced through the supporting structure of the wall of the gallbladder to become branched with a small neck communicating with the inner aspect of the organ. The frequency of the occurrence of these sinuses was demonstrated in a review by one of us (Moore [5]); 300 gallbladders removed at operation were examined and 101, or one third, were observed to have recognizable Rokitansky sinuses. Ninety-seven per cent of these gallbladders contained stones.

When a simple sinus becomes a branched diverticulum with a small neck, changes within the wall of the gallbladder or within the sinus itself may result in occlusion of this outlet. Such conditions arise during the change in the wall associated with acute diffuse inflammation of the gallbladder, obstruction of the cystic duct and impairment of the circulation of the lymphatic drainage. With any of these, a Rokitansky-Aschoff sinus which has developed into a diverticulum and then undergone occlusion becomes a potential abscess. If the gallbladder contains bacteria, the occluded Rokitansky-Aschoff sinus also probably will, and thus the abscess increases and extends as a result of the bacterial action. As the small abscess increases in size, it extends in the line of least resistance, which is usually toward the periphery. If the periphery is covered by peritoneum, a sufficient degree of resistance may be encountered to prevent rupture. If, however, there is no peritoneum, as in the hepatic portion of the gallbladder, perforation through the wall takes place rather rapidly. The abscess, no longer confined within the gallbladder wall, may extend between the gallbladder and the liver or through the liver to form a subphrenic abscess. If the process is sufficiently rapid, perforation through the peritoneal surface of the gallbladder may take place. This would, of course, be a free perforation into the peritoneal cavity, were it not for the high efficiency of the omentum and the regional viscera, which tend to wall the abscess off as soon as perforation becomes imminent.

The association of the Rokitansky-Aschoff sinus with long-standing infection and calculi in the gallbladder proper and the rarity with which perforation of the gangrenous gallbladder wall occurs when infection and calculi have not preexisted indicate that such a mechanism may frequently be involved. Furthermore, such a mechanism could account for the multiple perforations of the gallbladder which are occasionally encountered.

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5. Moore, S. W.: Intramural Formation of Gallstones, Arch. Surg. **34**:410-423 (March) 1937.

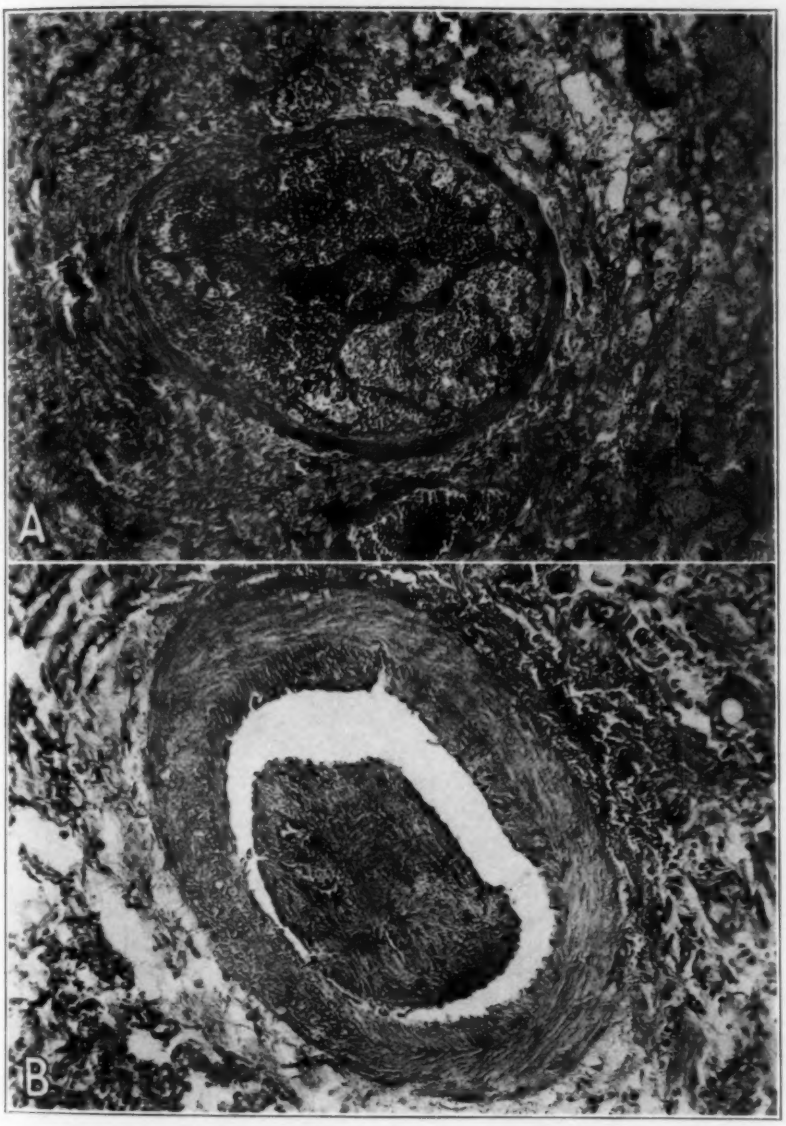

Fig. 2.—*A*, photomicrograph (× 97) of an artery in the wall of a gallbladder showing thrombosis with invasion of the thrombus by polymorphonuclear leukocytes. *B*, photomicrograph (× 110) of an artery with an organized thrombus and recanalization. We interpret this as the end process of that shown in *A*.

Gangrenous cholecystitis has been observed to occur after unrelated surgical operations. A case was reported by Kocher,[6] in which acute cholecystitis developed in a 51 year old woman eight days after repair of a ventral hernia. In another case, reported by Duncan, the condition followed operation on a woman with strangulated femoral hernia and intestinal obstruction. The patient died, and postmortem examination showed a gangrenous perforated gallbladder with generalized biliary peritonitis. No stones were found. W. A. Fisher[7] reported the case of a 19 year old football player who was operated on for reduction of the scaphoid bone. Acute gangrenous cholecystitis developed two days later. No stones were found, and he recovered. One of us (Glenn) recently saw a patient in whom gangrenous cholecystitis developed with free perforation five days after operation for hydrocele.

Gangrene of the gallbladder is not unusual and occurs far more frequently than one is generally disposed to assume. Over a period of slightly more than eight years we have observed in the New York Hospital 84 patients on whom a diagnosis of gangrene of the wall of the gallbladder according to the aforementioned definition was made. By and large, this condition has been accurately diagnosed under the general term of acute cholecystitis. In this period almost 350 patients were subjected to surgical treatment for acute cholecystitis. Preoperatively, it is probably impossible to differentiate acute cholecystitis, empyema of the gallbladder and gangrene of the gallbladder. The clinical manifestations of a progressive process are sometimes entirely lacking. Examples have been encountered in which a patient over 50 years of age has had only slight elevation of temperature and minimal leukocytosis with a palpable mass in the right upper quadrant of the abdomen but at operation has been found to have a gangrenous gallbladder.[8] On the other hand, it has been more frequently observed that when the patient's temperature rises and the leukocyte count increases during a period of observation, at operation progressive gangrene of this organ is found.

In this series of 84 patients with gangrene of the gallbladder wall there are 44 women and 40 men—a far higher incidence among men than is noted with regard to the general occurrence of the disease, for in a series of almost 1,500 patients subjected to operation for nonmalignant disease of the biliary tract the ratio was 1 man to 4-5 women. The gallbladders of 5 of these men did not contain calculi, while calculi were found in the gallbladders of all the women. One of the 5 men was operated on some three years later, and a stone was removed from

6. Kocher, T., and Matti, H.: Ueber 100 Operationen an den Gallenwegen mit Berücksichtigung der Dauererfolge, Arch. f. klin. Chir. **81**:655, 1906.

7. Fisher, W. A., cited by Vest.[2]

8. Glenn, F.: Acute Cholecystitis, Surg., Gynec. & Obst. **69**:431-435, 1939.

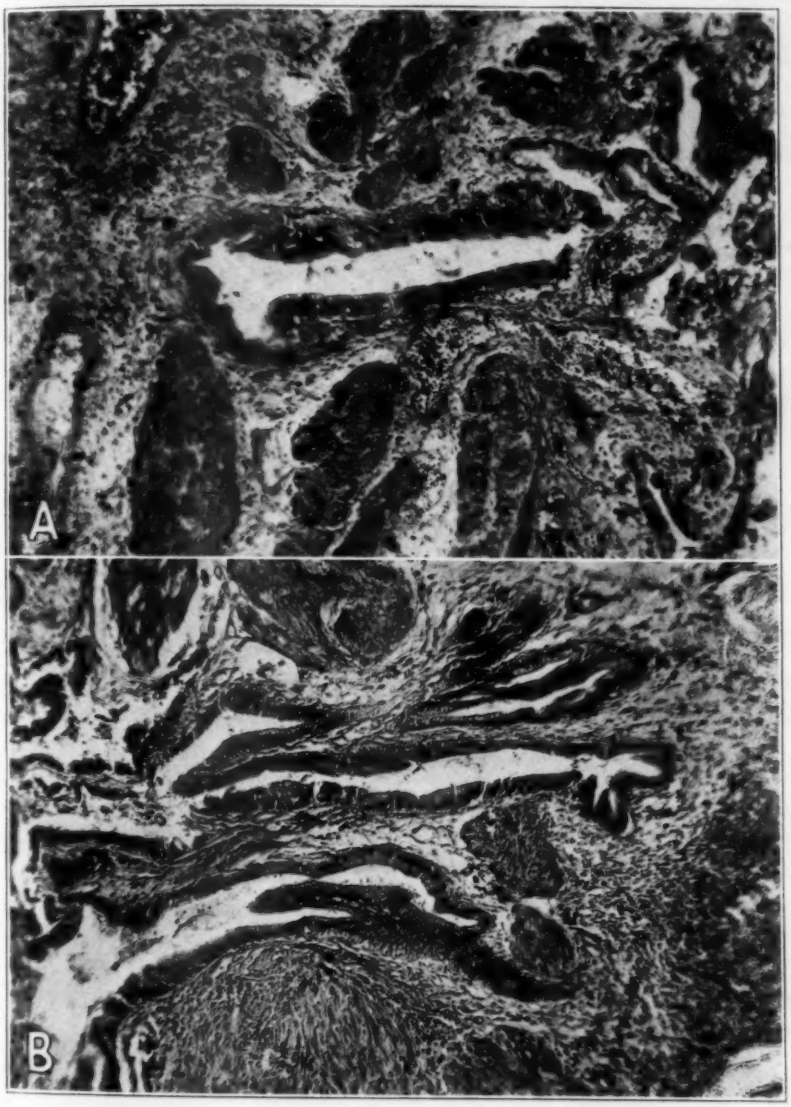

Fig. 3.—*A*, photomicrograph (× 100) of a Rokitansky-Aschoff sinus which has completely penetrated the muscularis. This we believe is the result of increased intracystic pressure and decreased resistance in the gallbladder wall. There are many lymphocytes, suggestive of the degree of inflammation in this area. *B*, photomicrograph (× 78) of the mucosa of the lumen of a gallbladder continuous with a Rokitansky-Aschoff sinus which has penetrated the muscular layer.

the common duct. It might be assumed in this particular instance that the gallbladder contained small stones which passed into the common duct. Forty of the 44 women had undergone one or more pregnancies. The youngest patient was 9 and the oldest 73. In the majority of instances gangrene of the wall of the gallbladder occurred after the beginning of the fifth decade. Of the total of 84 patients there were 59 who had symptoms of gangrene of the wall of the gallbladder without evidence of perforation. In the majority of these, however, the omentum, as well as the adjacent viscera, had become adherent to the organ. In 22 patients there was perforation with localized peritonitis or localized abscess. There were many instances in which there were multiple gangrenous areas of the gallbladder with more than one perforation. These perforations resulted in abscess between the gallbladder and the liver, between the gallbladder and the omentum and also the viscera. There was 1 instance of perforation into the transverse colon and the duodenum. There were 3 patients with free perforation into

TABLE 2.—*Average Age of Eighty-Four Patients with Acute Gangrenous Cholecystitis*

Patients	Condition	Average Age
3	Free perforations	56
22	Perforations and abscess	50
59	Gangrenous cholecystitis	44

the peritoneal cavity. Two of these patients died, whereas only 3 of the remaining 81 patients died.

The purpose of reporting this series of patients with gangrene of the wall of the gallbladder is to emphasize the advisability of the surgical treatment of the patient with acute cholecystitis. In a review of our total experience with this disease we have concluded that we are unable to distinguish acute cholecystitis, acute cholecystitis with gangrene and perforation which has resulted in a walled-off abscess. Free perforation into the peritoneal cavity of a gangrenous gallbladder is rarely recognized early enough to save the patient's life; this is evidenced in 3 patients in whom we found free perforation and among whom the mortality rate was 66 per cent.

One of the deaths reported in this series was that of a child with typhoid fever. The removal of the gangrenous gallbladder unfortunately did not favorably influence the course of the disease, and it is probable that the removal of the gallbladder had little to do with the peritonitis from which the patient died. Fortunately, typhoid fever is rare in this era and therefore should probably not be considered in this series of patients. A 41 year old patient died on his sixth postoperative day from pneumonia. This death is to be credited to the operative pro-

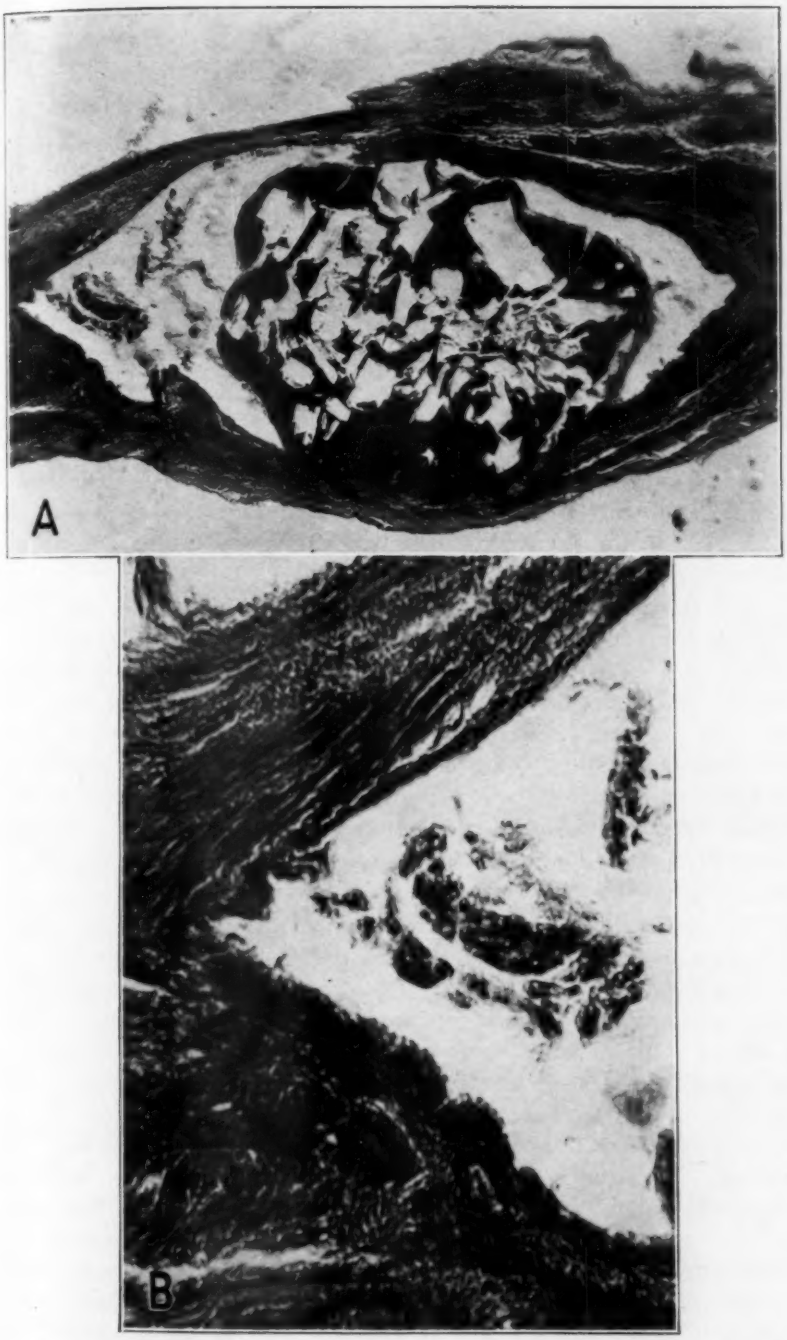

Fig. 4.—*A*, photomicrograph (× 97) of a thin gallbladder wall which contained a tremendously dilated Rokitansky-Aschoff sinus that had penetrated the muscularis. This sinus contained an intramural gallstone. That it is lined with mucosa is demonstrated in *B*, a higher magnification (× 331).

cedure and not to the course of the disease, although this patient might have continued on to free perforation and peritonitis. A third patient, a 50 year old woman, had neglected gangrenous cholecystitis with perforation and localized peritonitis which had extended to become a subdiaphragmatic abscess. Perforation through the diaphragm into the pleural cavity resulted in empyema and death. Earlier operation would have prevented this unfortunate course of events. The remaining 2 deaths were those of patients with free perforation and generalized peritonitis; 1 was 50 years of age and the other 65. These 2 patients represent the group in which free perforation is most likely to occur. Thus, acute cholecystitis in patients over 50 at once becomes a more serious disease than acute cholecystitis in patients under 50. If one is to employ surgical therapy for patients under the age of 50, then it should be urged much more forcefully for those over 50, because it is in this group that perforation and free perforation are most likely to occur. It is these complications that carry with them the highest mortality rate.

The treatment of acute cholecystitis with gangrene does not differ from that of acute inflammation of the gallbladder. It is advisable to remove the gallbladder, provided the patient's general condition and local complications do not contraindicate such a procedure. In this series of patients, 77 were subjected to cholecystectomy, 6 to cholecystostomy, and 1 patient was not operated on. Cholecystostomy is generally reserved for those patients in whom cholecystectomy is contraindicated. Therefore, these patients are the more ill, and the associated high mortality rate is indicative of the severity of the disease rather than of the risk of the type of procedure employed.

The differential diagnosis between biliary colic, acute cholecystitis and other acute conditions commonly found in the right upper quadrant of the abdomen taxes the diagnostic acumen of the most experienced abdominal surgeon. Because perforated ulcer, acute appendicitis or acute pancreatitis may lead to death if surgical intervention is withheld, a differential diagnosis appears less important than an attitude which leads to surgical treatment. Without an attitude that provides for the surgical treatment of acute cholecystitis there may be justification for both practitioner and surgeon to permit certain of these acute abdominal conditions to progress into their terminal phase without operation. Perhaps free perforations into the peritoneal cavity following acute cholecystitis occur because a policy of operating on all patients is not more generally held. Zollinger [9] has correctly insisted that each patient with acute cholecystitis should be considered as an individual surgical problem. With this we agree, for all surgical problems are such.

9. Zollinger, R.: Acute Cholecystitis, New England J. Med. **224**:533-537, 1941.

DUPUYTREN'S CONTRACTURE

A CONSIDERATION OF THE ANATOMY OF THE FIBROUS STRUCTURES OF THE HAND IN RELATION TO THIS CONDITION, WITH AN INTERPRETATION OF THE HISTOLOGY

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The material of the present study has been evaluated under three headings: (1) the gross anatomy of the human palmar fascia as revealed in a study of 60 hands presenting no gross abnormality of this structure; (2) the microscopic anatomy of the palmar fascia in 27 grossly normal hands, and (3) the histology of the tissue removed in 35 cases of Dupuytren's contracture.

GROSS ANATOMY OF THE NORMAL HUMAN PALMAR FASCIA—ITS RELATION TO THE DEVELOPMENT AND THE SURGICAL CORRECTION OF THE DEFORMITY IN DUPUYTREN'S CONTRACTURE

The material consisted of 60 hands from 30 cadavers of men between 22 and 85 years of age. It was felt that the anatomic descriptions should include not only the superficial palmar layer and its attachments but also the deep interosseous fascia and the interfascial septums. All of these structures bear an intimate relation, proximally, to the fascial structures of the volar surface of the wrist and the forearm, and, distally, to the fascial and ligamentous structures of the fingers. As emphasized by Kanavel, Koch and Mason,[1] these anatomic facts have an important bearing on the development and the surgical correction of the deformity in Dupuytren's contracture.

In the material studied it was found that the superficial palmar fascia merged, proximally, with the palmar surface of the transverse carpal ligament and with the tendon of the palmaris longus muscle or, in

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1. Kanavel, A. B.; Koch, S. L., and Mason, M. L.: Dupuytren's Contraction, with a Description of the Palmar Fascia, a Review of the Literature and a Report of Twenty-Nine Surgically Treated Cases, Surg., Gynec. & Obst. **48**:145-190, 1929.

the absence of the latter, with the antebrachial fascia. Distally, its longitudinal fibers broke up into longitudinal bands (the pretendinous bands). Fibers extended into the deep surface of the skin along the entire length of the pretendinous bands and were especially developed over the region of the metacarpophalangeal joints. A thin fascial extension covered the interdigital spaces in which the digital nerves and vessels became more superficial. Between these distinct bands there were deeper, intertwining transverse fibers which became most distinct in the region of the distal transverse palmar crease and again in the region of the finger webs (the natatory ligaments). These transverse fibers were found to be intimately attached to the fibrous tendon sheaths of the fingers and to the deep surface of the overlying skin. Laterally and medially, the superficial palmar fascia thinned out where it overlay the thenar and hypothenar muscle groups (fig. 1).

The number and the arrangement of the pretendinous bands varied considerably. This variation was demonstrated by Kalberg [2] in an extensive series of 400 palmar fascia specimens (234 from the right hand, 166 from the left). He found that the number and the arrangement of the pretendinous bands varied as follows:

Three bands in 2 per cent of the specimens to the second, third and fifth fingers

Four bands in 24 per cent of the specimens to the second, third, fourth and fifth fingers

Five bands in 18 per cent of the specimens to the first, second, third, fourth and fifth fingers

Five bands in 31 per cent of the specimens—single bands to the third, fourth and fifth fingers; double band (split) to the second finger

Six bands in 14 per cent of the specimens—single bands to the third and fifth fingers; double bands (split) to the second and fourth fingers

Seven bands in 11 per cent of the specimens—single bands to the first, third and fifth fingers; double bands to the second and fourth fingers

Fibers from the deep surface of each longitudinal band merged with the fibrous sheath of the flexor tendons and could be traced for a variable distance along the superficial layer of the sheath as far distalward as the middle phalanx. The latter portions of each longitudinal band formed two distinct lateral bands at the webs, which gained attachment to the sides of the flexor tendon sheaths, to the capsule of the metacarpophalangeal joint and to the periosteum of the proximal phalanx and which were intimately related to the aponeurotic expansion of the extensor tendon and to the insertion of the interosseous and lumbrical muscles.

The volar interosseous fascia covered the palmar interosseous muscles and communicated with the superficial fascial layer by vertical septums which formed the fascial compartments of the hand. Proximally,

2. Kalberg, W.: Zur Anatomie der Palmaraponeurose, Anat. Anz. **81**:149-159, 1935.

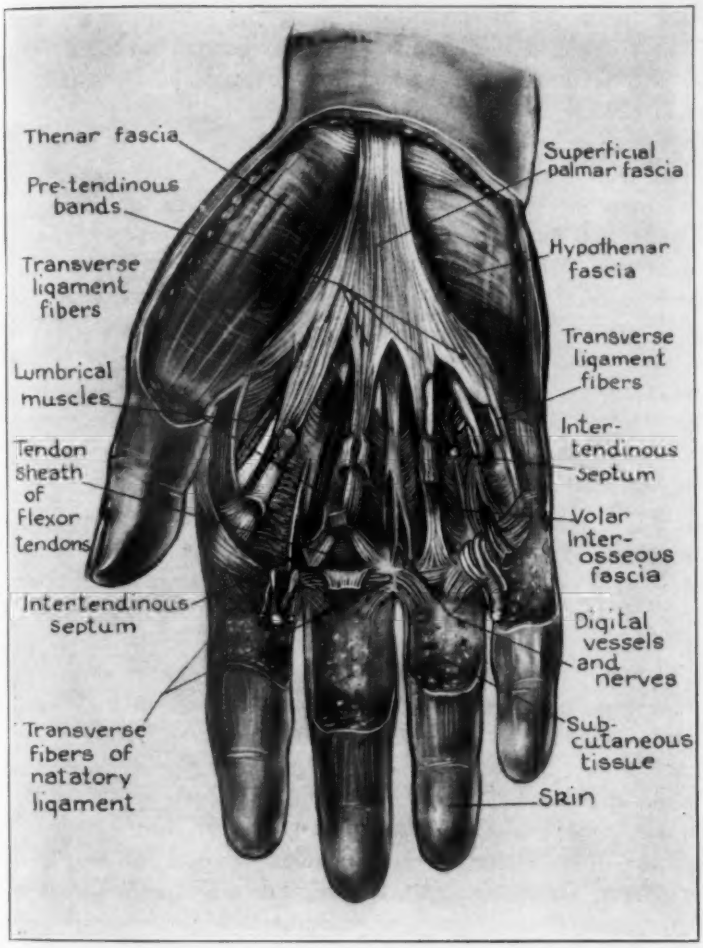

Fig. 1.—Drawing showing the gross anatomy of the palmar fascias and septums in the human hand. The superficial stratum merges, proximally, with the superficial fibers of the transverse carpal ligament; it extends laterally and medially as a thin sheath over the thenar and hypothenar muscle groups and divides distally into the pretendinous bands. The ring finger illustrates the distal longitudinal and transverse fibers of this layer as they terminate in the subcutaneous layer of the proximal portion of the finger. In the middle and index fingers, the pretendinous band and the transverse ligaments have been sectioned and reflected to demonstrate the deep fibers extending from the pretendinous band to the fibrous tendon sheath of the flexor tendons and the lateral extensions of this band into the base of the finger. The intertendinous septums and their attachments to the interosseous fascia and at the base of the fingers are also illustrated.

this deep fascial layer was continuous with the ligamentous structures on the volar surface of the wrist and the pronator quadratus muscle. Its transverse fibers became thickened opposite the metacarpal heads to form the transverse metacarpal ligament, and distally, it merged with the volar portion of the capsule of the metacarpophalangeal joint, the digital fibrous sheath of the flexor tendons and the periosteum of the proximal phalanges (fig. 1).

The three main vertical septums (intertendinous or paratendinous septums) were attached to the metacarpal bones and could be traced distalward to the digital fibrous tendon sheaths, to the capsule of the metacarpophalangeal joints and to the lateral aspects of the proximal phalanges (fig. 1).

In the available material it was not possible to demonstrate with satisfaction, even in cross sections of several whole hands, the vertical fibers described by Legueu and Juvara [3] as extending from the pretendinous bands to the dorsum, between the metacarpal heads, becoming attached to the dorsal aponeurosis of the hand and forming sheaths for the interosseous muscles.

Comment.—The deformity in Dupuytren's contracture must depend, at least in part, on such factors as (1) the preexisting anatomic structure of the palmar fascia and (2) the extent of involvement not only of the superficial layer but also of all the related fascial layers and septums. Involvement of those fibers between the superficial fascial stratum and the skin leads to induration and puckering of the skin and to accentuation of the transverse palmar creases; this deformity, clinically, precedes finger deformities. The presence or the absence of pretendinous bands to certain fingers and the extent of their anatomic development, must predetermine, at least in part, which fingers will become deformed and the extent of this deformity. Flexion deformities, however, will be caused not only by involvement of these longitudinal bands—by virtue of their attachment to the skin and to the fibrous tendon sheaths—but also by the vertical septums and by the volar interosseous membrane, the fibers of which merge, distally, with the digital fibrous sheaths of the flexor tendons, the capsule of the metacarpophalangeal joints and the periosteum of the proximal phalanges. These flexion deformities of the fingers may become exaggerated by secondary shortening of the volar capsules of the metacarpophalangeal and the proximal interphalangeal joints and of their collateral ligaments and by adaptive shortening of the flexor tendons themselves.

The amount of operation (i. e., excision of the involved fascias) necessary to effect and maintain good correction of the deformities in

3. Legueu, F., and Juvara, E.: Des aponévroses de la paume de la main, Bull. Soc. anat. de Paris **67**:383-400, 1892.

Dupuytren's contracture will depend also on these anatomic features. It has been the experience of most contemporary surgeons, as well as my own in the series herein reported, that treatment must consist of wide excision not only of the contracted superficial palmar fascia and its digitations but also of the attachments to the skin, the paratendinous septums and even the distal portions of the deep interosseous fascia. The correction of flexion deformities of the fingers may necessitate widespread excision and division of soft tissue and even resection of bone. Since this amount of operation has sometimes led to a functionally useless digit, the wisdom of immediate amputation of a severely deformed finger has become apparent.

MICROSCOPIC ANATOMY OF THE SUPERFICIAL PALMAR FASCIA IN HUMAN HANDS PRESENTING NO GROSS ABNORMALITY OF THIS STRUCTURE

Histologic preparations were made from both the palmar and the digital portions of the superficial palmar fascia from 27 cadaver specimens. Three of these specimens were from fetuses at the stage of 3, 6 and 9 months, respectively. The remaining 24 were obtained from 20 adult human cadavers whose ages varied between 16 and 85 years. Of these 20, 18 were male and 2 female; 13 were white, and 7 were Negroes. The distribution according to age groups was, more specifically, as follows: in the second decade, 1; in the third, 1; in the fourth 1; in the fifth, 1; in the sixth, 2; in the seventh, 8; in the eighth, 4; and in the ninth, 2.

The histologic structure of the superficial palmar fascia in all the specimens was found to be not unlike that of capsular and tendon tissues. A tendency to increasing thickness of the fascia and to greater density and compactness of the parallel collagenous fibers was apparent in the older age groups.

Although the palmar fascia was not distinguishable as a distinct layer in the hand of the 3 month fetus, it was evident in the hands of the 6 and the 9 month fetus. The features of the cellular structure of this layer in the latter 2 specimens were not distinctly different from those of the deeper muscle stratum.

In the adult specimens, the palmar fascia consisted of bundles of dense poorly cellular connective tissue, arranged longitudinally in some areas and transversely in others. The collagenous fibers were compacted into parallel bundles and demonstrated flattened and elongated nuclei and occasional small vascular channels. These features were demonstrable uniformly in all the specimens of the various age groups. It appeared, however, in the specimens representing the later decades of life that the fascial layer became thicker and more dense and the bundles of collagenous fibers more compacted. The resemblance of

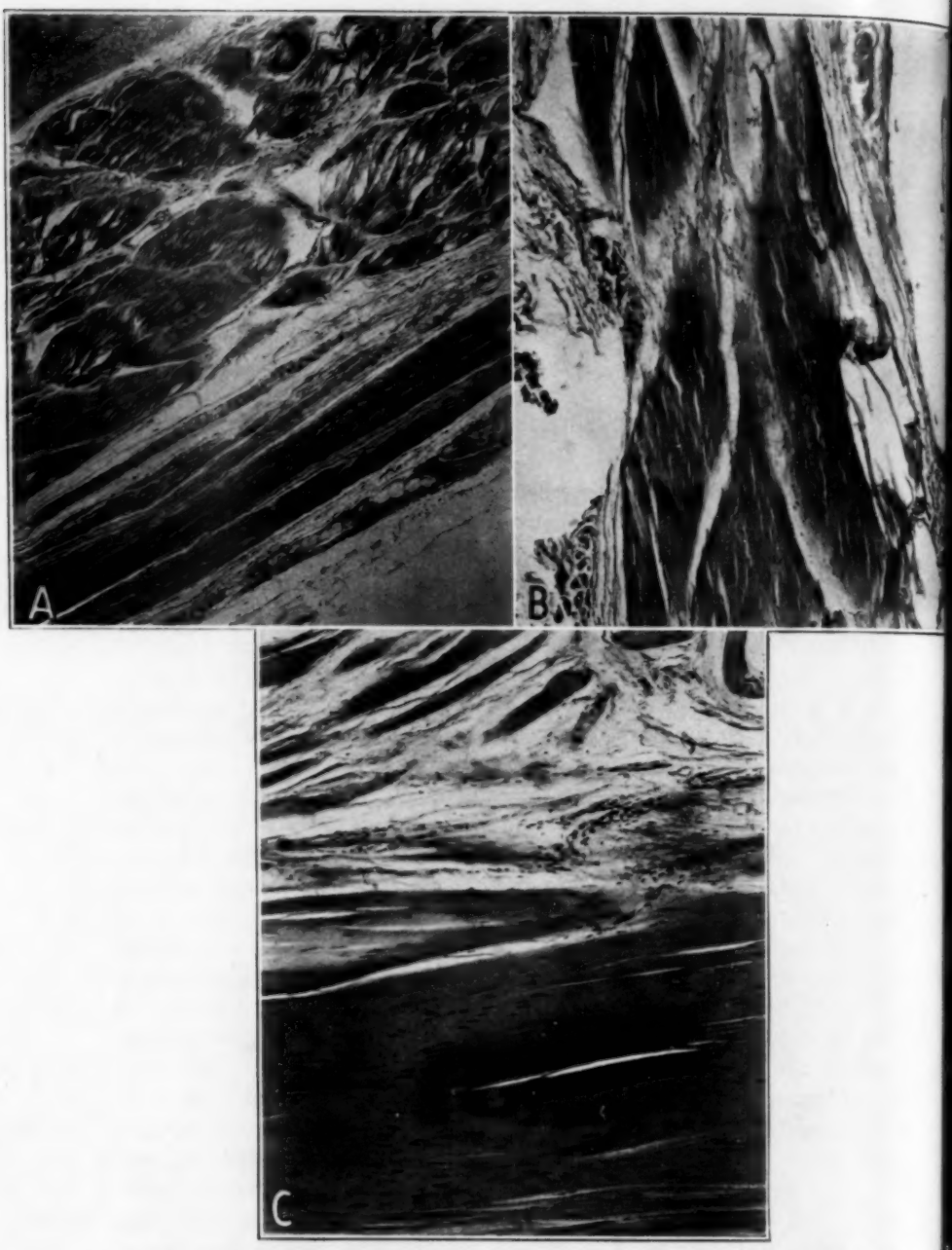

Fig. 2.—Photomicrographs showing: *A*, grossly normal palmar fascia (× 37) from the left hand of the cadaver of a white man aged 22 years; *B*, grossly normal palmar fascia (× 37) from the left hand of the cadaver of a Negro man aged 44 years; *C*, grossly normal palmar fascia (× 37) from the right hand of the cadaver of a white man aged 62 years.

this fascia, especially in the older specimens, to tendon tissue was striking. The histologic features bore no definite relation to the sex or race of the subject or to the side of involvement (figs. 2 and 3).

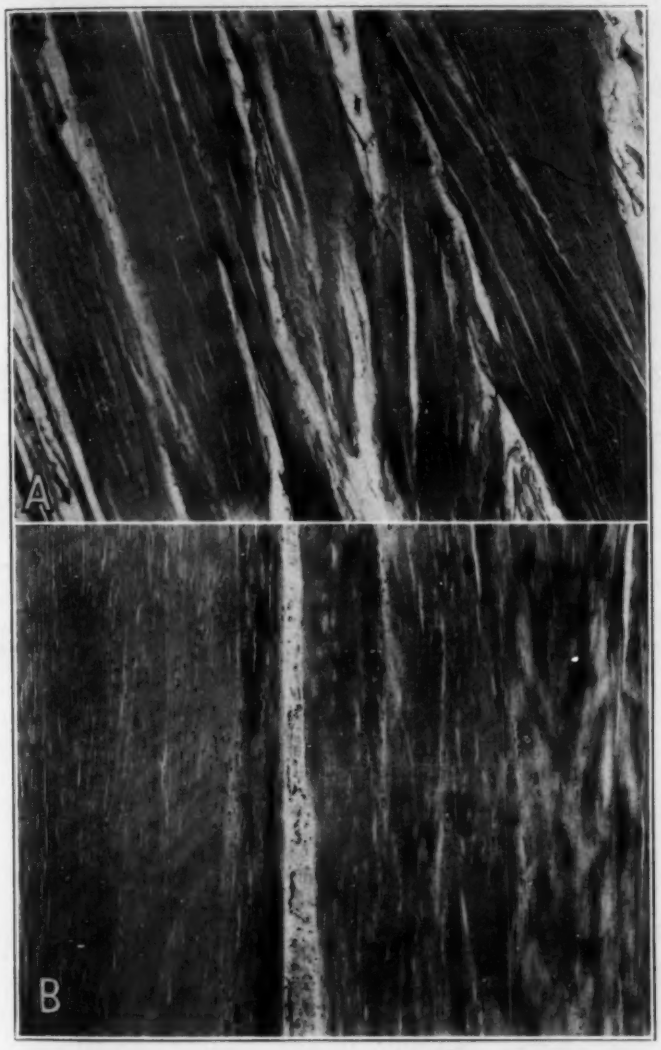

Fig. 3.—Photomicrographs showing: *A*, grossly normal palmar fascia (× 37) from the left hand of the cadaver of a white man aged 70 years; *B*, grossly normal palmar fascia (× 37) from the left hand of the cadaver of a white man aged 85 years. The fascial tissues shown in this and the preceding figure consist of bundles of parallel collagenous fibers with flattened elongated nuclei. In the older specimens, this tissue is less cellular and less vascular, while the collagenous fibers have lost their wavy character and become more closely compacted, thickened and hyalinized. This structure, especially in the older specimens, resembles that of tendon tissue.

Comment.—The histologic features of the palmar fascia in human fetuses and the histologic resemblance of this fascia to tendon tissue in adult human cadavers may be in keeping with the concept, defended by some anatomists, that the superficial palmar fascia represents the aponeurotic insertion of the palmaris longus muscle (when the latter is present). The theory, held by a few investigators, that this structure represents, in the human being, the tendinous counterpart of the atavistic muscle layer, the flexores breves manus superficialis, lacks sufficient supportive evidence.

The progressive thickening and condensation of the normal palmar fascia with advancing age may be of significance in the causation of Dupuytren's contracture, since this pathologic condition is most frequent in the later decades of life.

THE HISTOLOGY OF DUPUYTREN'S CONTRACTURE

The histology of Dupuytren's contracture has been extensively reviewed by Iklé,[4] Davis and Finesilver,[5] Ferrarini[6] and Meyerding, Black and Broders.[7] Most writers on this subject have recognized the essential process to be one of proliferation or hyperplasia of connective tissue, and they have noted the transition from the early features of a cellular tissue to the final stage of scarring. Some have interpreted this process as focal hypertrophy of connective tissue arising in the walls of the blood vessels. Others, without convincing evidence, have described the process as a chronic inflammatory one. Meyerding, Black and Broders[7] stressed the importance of chronic inflammatory changes in the skin, the subcutaneous tissue and the interstitial connective tissue, in association with the more generally recognized fibroplastic process involving the palmar fascia, and these authors have suggested that the disease begins in the interstitial connective tissue and spreads to involve the other tissues of the palm. The resemblance of certain cellular areas in Dupuytren's contracture to fibrosarcoma is purely superficial, and the evidence is distinctly against the idea of a neoplasm.

In general, I conclude from my findings that the essential pathologic changes are thoses of active fibroplasia involving the palmar fibrous

4. Iklé, C.: Zur Histologie und Pathogenese der Dupuytrenschen Kontraktur, Deutsche Ztschr. f. Chir. **212**:106-118, 1928.

5. Davis, J. S., and Finesilver, E. M.: Dupuytren's Contraction, with a Note on the Incidence of the Contraction in Diabetes, Arch. Surg. **24**:933-989 (June) 1932.

6. Ferrarini, M.: Sulla anatomia pathologica e sulla etiopatogenesi della malattia del Dupuytren, Arch. ital. di chir. **57**:1-110, 1939.

7. Meyerding, H. W.; Black, J. R., and Broders, A. C.: The Etiology and Pathology of Dupuytren's Contracture, Surg., Gynec. & Obst. **72**:582-590. 1941.

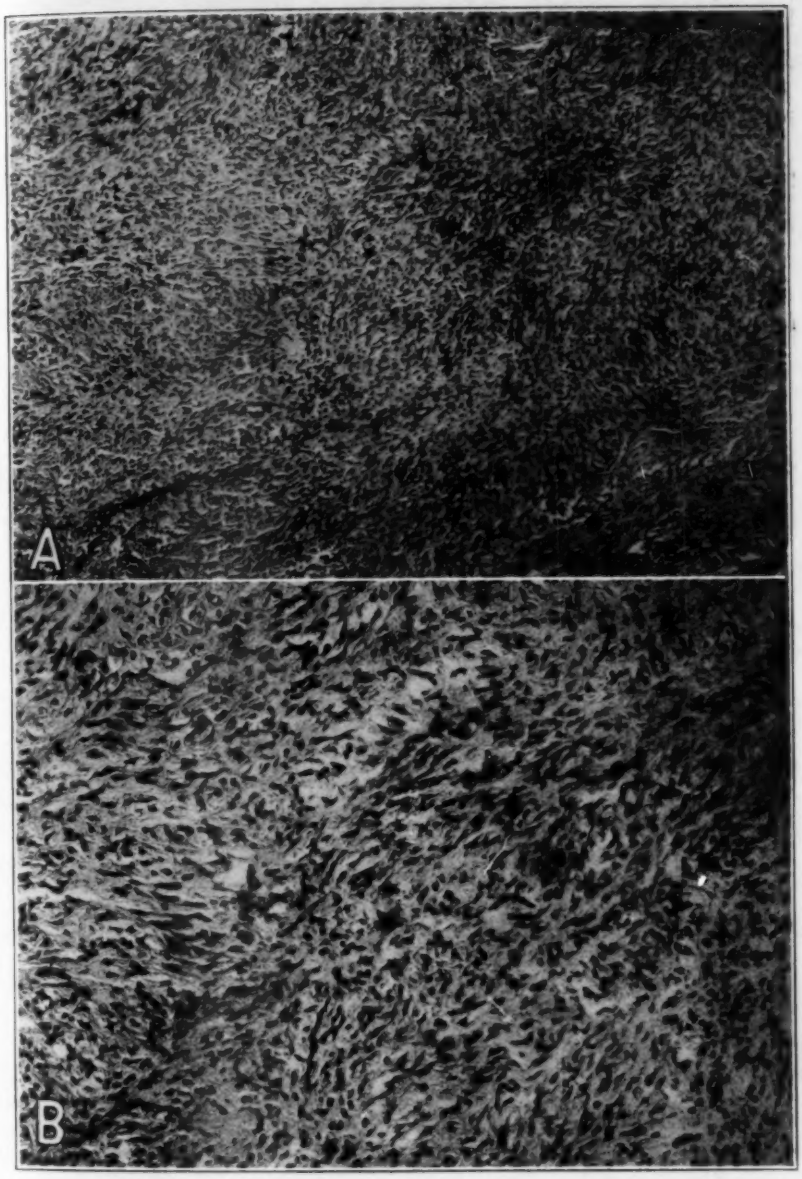

Fig. 4.—Photomicrographs showing: *A*, tissue (× 47) from the left hand of a 46 year old plasterer with Dupuytren's contracture of approximately ten years' duration. The tissue is hypercellular, and, especially in some areas, the nuclei are densely compacted, and there is little or no intercellular matrix. *B*, a section (× 94) from the center of the area illustrated in *A*. The nuclei are round, oval or elongated, stain deeply, and in some areas are closely compacted and form occasional multinucleated structures. The intercellular matrix is increased in the less cellular areas.

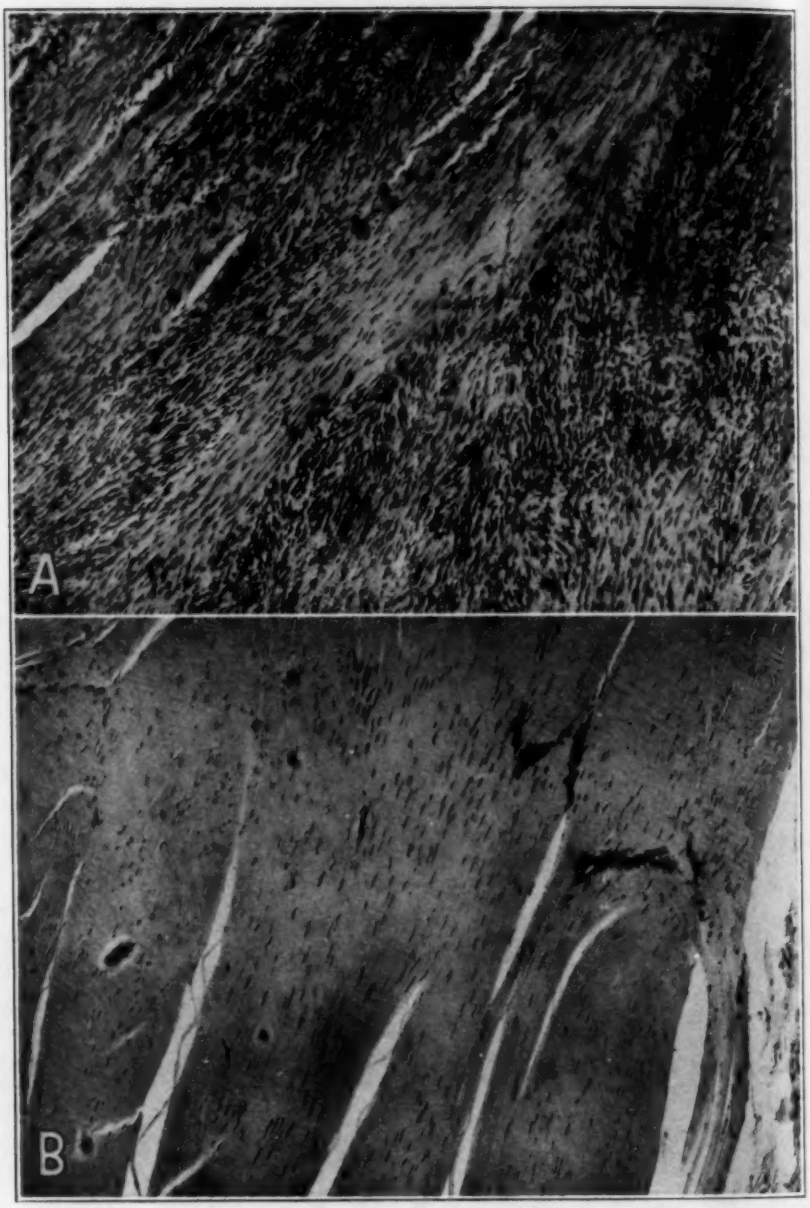

Fig. 5.—Photomicrographs showing: *A*, another area (× 47) in the same histologic preparation as that shown in figure 4. The tissue structure varies from that of hypercellular regions of irregular structure through less cellular areas with more intercellular matrix and a tendency for the parallel arrangement of fibroblasts to poorly cellular areas in which the intercellular tissue predominates and in which the nuclei are much flattened and elongated. *B*, another area (× 47) from the same histologic preparation as that shown in figure 4. In this region the parallel collagenous fibers are densely compacted and hyalinized, and the nuclei are sparse, flattened and elongated, so that the structure is identical with that of tendon tissue.

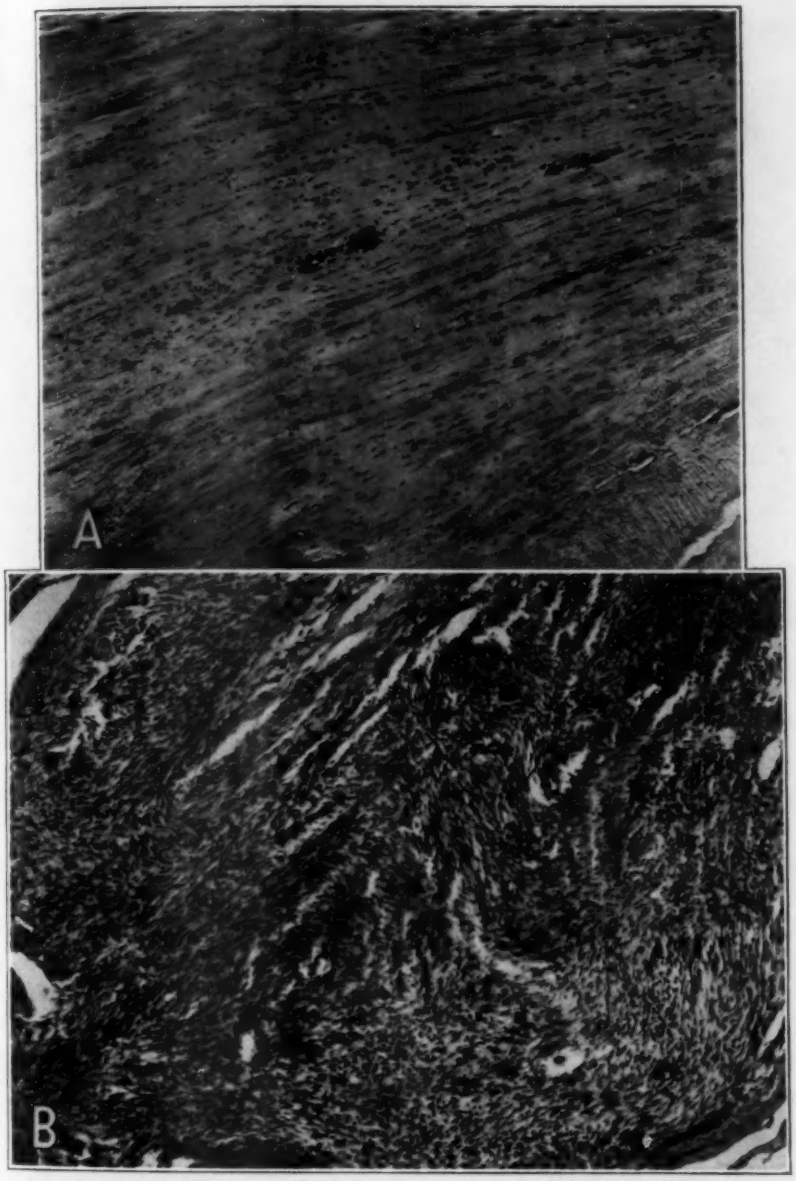

Fig. 6.—Photomicrographs showing: *A*, tissue (× 50) from the right hand of a 47 year old painter with Dupuytren's contracture of approximately three months' duration. The connective tissue is densely compacted and poor in cells and resembles capsular or tendon tissue. *B*, tissue (× 44) from the left hand of a 53 year old watchman with Dupuytren's contracture. The deformity had been present for approximately twenty years. The tissue is hypercellular and shows closely compacted round and oval nuclei and little intercellular matrix. Although there is active fibroplasia, there are no mitotic figures, and the lobule of tissue illustrated is clearly delimited by a zone of dense fibrous tissue. That the histologic activity bears no definite relation to such clinical features as the duration of the pathologic process is demonstrated in cases such as these.

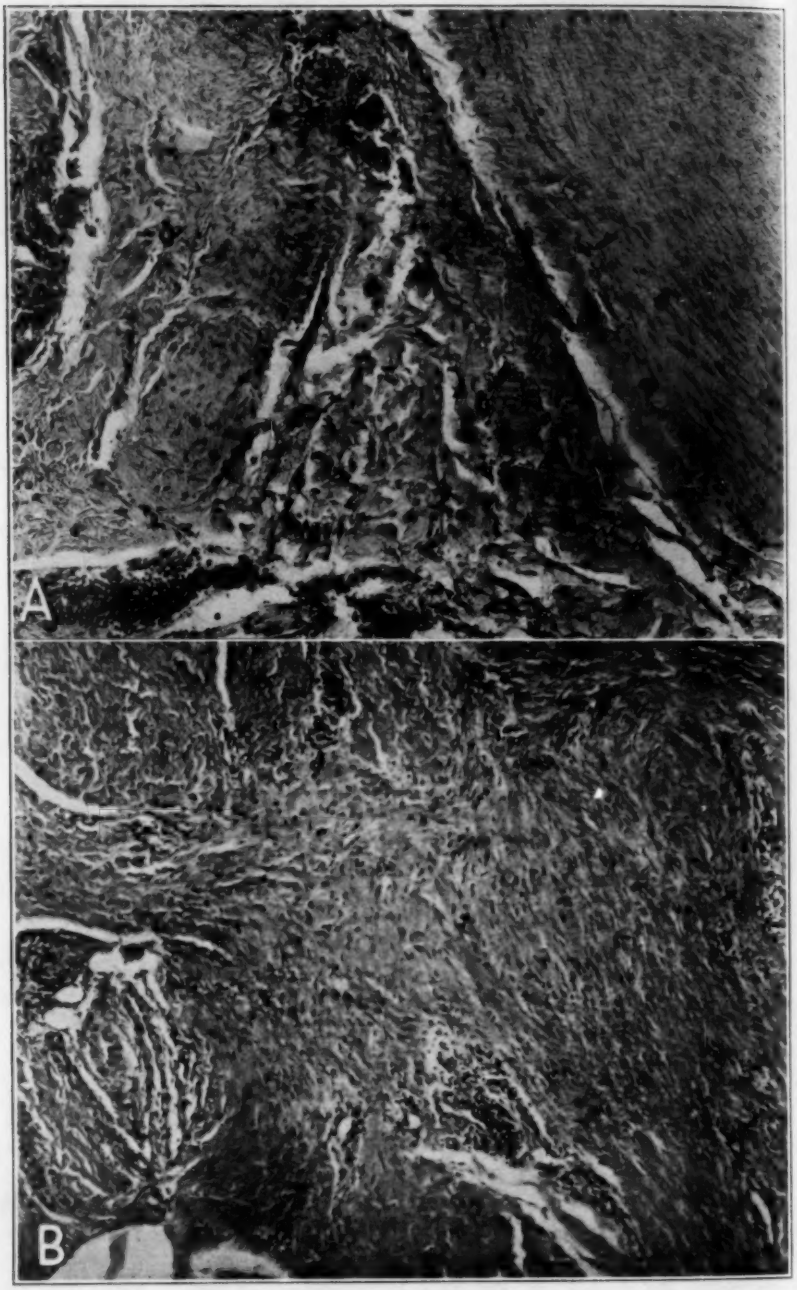

Figure 7

(See legend on opposite page)

tissues, of which the palmar aponeurosis is the chief constituent. Associated changes were present also in the skin and the subcutaneous tissues and involved the vessels and the tendon sheaths. This proliferative process was interpreted as benign local fibroplasia which terminated in the final picture of avascular scarring. Inflammatory features were not constant. The cellular proliferation was uniform and orderly, and there was no evidence of invasiveness. No definite correlation between the clinical and the histologic features of Dupuytren's contracture could be ascertained.

The clinical features in this series of 35 cases were identical with those reported by previous authors. The age distribution was as follows: 30 to 39 years, 3 cases; 40 to 49, 12; 50 to 59, 14; 60 to 69, 6. The youngest patient was 30 years of age and had had the deformity for about four years; the oldest was 68 and had had the deformity for about four months. Thirty-three of the patients were male, and 2 were female. In only 18 of the 35 cases was the patient engaged in an occupation in which the involved hand might have been subjected to repeated trauma. The disorder was bilateral in 19 cases (more advanced on the right in 8; more advanced on the left in 6; equal in 5) and unilateral in 16 (in the right hand in 12; in the left hand in 4). The deformity present consisted only of thickening of the palm in 4 of the 54 hands, while palmar deformity was associated with deformity of one or more fingers in the remaining 50 hands—the fourth or fifth fingers or both being involved in all of these hands; the third in 7; the second in 1, and the thumb in 1. The history of the duration of the deformities prior to treatment varied from a minimum of three months to a maximum of twenty years. There was associated gout in 1 case, diabetes mellitus in 1 case and polyarthritis in 2 cases. In the remaining cases, all clinical and laboratory findings were normal.

The patient usually stated that he or she had noted a small nodule or induration followed by puckering of the palmar skin—most often

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EXPLANATION OF FIGURE 7

Photomicrographs showing: *A*, tissue (× 50) from the left hand of a 55 year old barber with Dupuytren's contracture. The contracture was of approximately seven years' standing. The fibrous tissue is uniformly dense but moderately cellular. Large aggregates of lymphocytes, usually arranged about the periphery of blood vessels, constitute a prominent feature. *B*, tissue (× 50) from the right hand of a 36 year old clerk with Dupuytren's contracture. The contracture had been noted for only three months. The histologic features in this section are identical with those of *A*. That these areas of perivascular lymphocytic infiltration, when present, bear no definite relation to such clinical features as age of the subject and duration of the pathologic process or to other more constant histologic features is demonstrated in cases such as these.

at the base of the fourth and fifth fingers—which was followed months or years later by the development of flexion contracture of the affected finger, associated with the appearance of a thickened band extending from the concavity of the palm to as far as the proximal interphalangeal joint of the involved finger. Later, implication of adjacent fingers was noted together with the appearance of more nodules and funnel-like depressions of the palm, further induration and creasing of the skin and atrophy of the subcutaneous tissues. In only 2 cases was there a history of brief tenderness of the involved palm and finger.

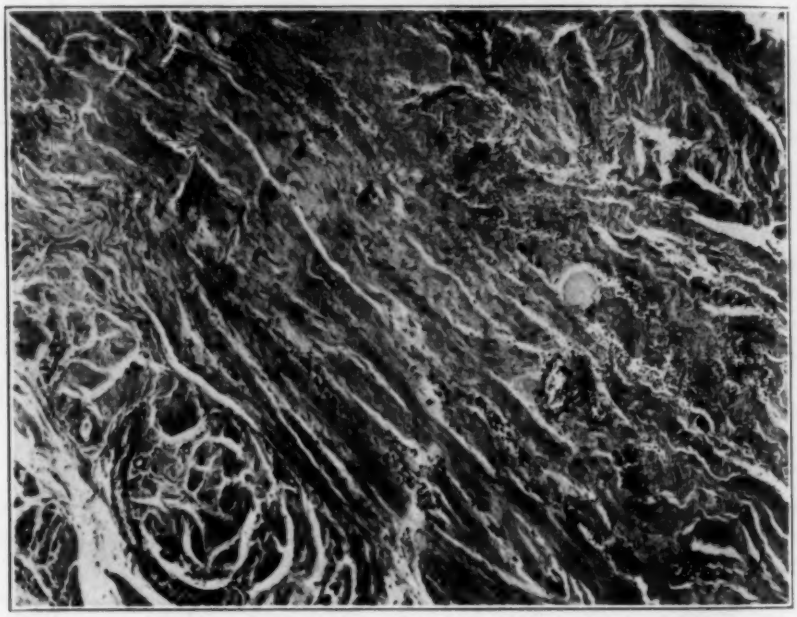

Fig. 8.—Photomicrograph showing tissue (× 47) from the right hand of a 30 year old truck driver with Dupuytren's contracture of approximately four years' duration. The deformity recurred six months after incomplete excision. The tissue illustrated was obtained at the first operation. In the main, it is composed of compacted and hyalinized fibers in which the nuclei are flattened and elongated. About some of the blood vessels there are collections of cells which are not inflammatory but which represent localized areas of hypercellularity in the perivascular connective tissues. As demonstrated in this case and in others, the incidence of recurrence appears to bear no definite relation to the histologic activity of the involved tissues.

In all 35 cases, the involved fascias were subjected to surgical excision. Recurrence took place in 6 cases—after obviously incomplete operation in 3 and after extensive and apparently complete operations in the other 3.

As to the microscopic findings, specimens in which portions of the skin overlying the contracted fascia were available showed widespread involvement of the skin and subcutaneous tissue in addition to the changes in the aponeurosis. The epidermis was hypertrophied and keratinized and the corium intensely affected by fibrosis, while the papillae had disappeared. There were scattered collections of lymphocytes concentrated especially within and just beneath the corium. The subcutaneous adipose tissue was diminished or almost absent and contained scattered blood vessels and sweat glands.

In the deeper layers there were large collections of cellular tissue with little or no stroma. The closely compacted nuclei in these hyper-

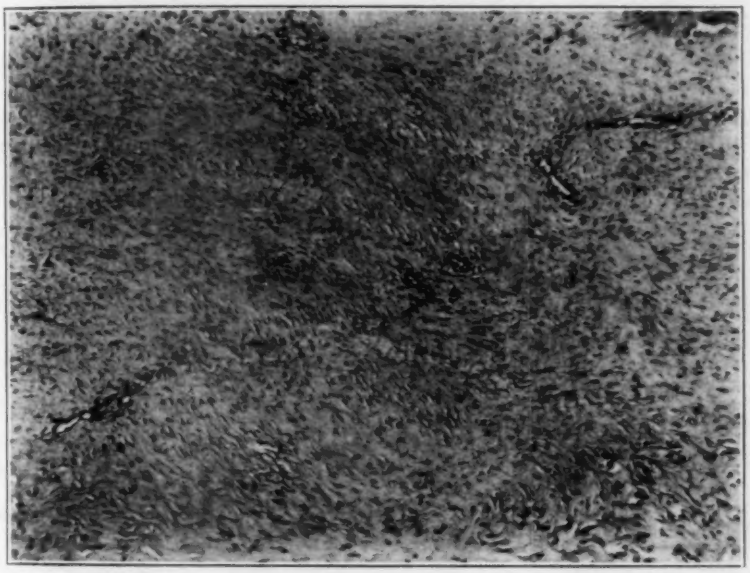

Fig. 9.—Photomicrograph showing a section (× 50) of a painful nodule removed from the plantar fascia of the right foot of a 48 year old woman. There were several such nodules in the plantar fascia of both feet, but the palmar fascias were apparently uninvolved. This area represents cellular noninflammatory connective tissue hyperplasia. The histologic structure is similar to the fibroplasia occurring with Dupuytren's contracture (compare with fig. 4 *A*). In other regions (not shown) the connective tissue was more mature and had undergone hyalinization in places.

cellular areas were round or oval and stained deeply. Rarely, a mitotic figure was noted. Such areas were interpreted as representing actively proliferating tissue. They tended to be arranged in lobules, the tissue increasing in maturity from the center to the periphery, and these lobules were delimited from the surrounding tissues by a zone of fibrous poorly cellular connective tissue (figs. 4 and 6 *B*). In other regions, the connective tissue cellularity was less marked, and there

was a greater amount of intercellular matrix. The nuclei in such areas were spindle shaped or elongated and flattened, and the cells tended to be arranged in parallel masses (fig. 5). In still other areas, the collagen fibers were hyalinized and closely compacted, and the nuclei were considerably thinned and elongated. This fibrosis and scarring progressed even to the extent of producing resemblance to tendinous tissue (figs. 5 *B* and 6 *A*).

In most instances, these variations in connective tissue cellularity were recognizable within the same specimen (figs. 4 and 5). The

Fig. 10.—Photomicrograph showing a section (× 50) from a keloid of the left ear of a 36 year old Negro woman, which had arisen after piercing of the lobule ten years previously. The tissue is densely fibrous; the collagenous fibers are arranged in parallel bundles with flattened nuclei and few blood vessels. Scattered collections of lymphocytes are evident about the periphery of some of the vessels. The structure is tendon-like and closely resembles the more mature areas in cases of Dupuytren's contracture.

growth was uniform and orderly, and there was no indication of invasiveness. In some regions, especially between the lobules of cellular tissue, the connective tissue was loose and relatively vascular. In such areas in some of the specimens, collections of lymphocytes were

demonstrable, but this feature was inconstant. These collections, when present, were usually but not always perivascular in arrangement (fig. 7).

Similar connective tissue hyperplasia was observed in the plantar fascia of a subject in whom there was no demonstrable palmar involvement (fig. 9). Although there was no record of clinical involvement of the plantar fascias in the 35 cases of Dupuytren's contracture in this study, it should be borne in mind that the generous subcutaneous adipose tissue and thick skin of the sole of the foot might interfere

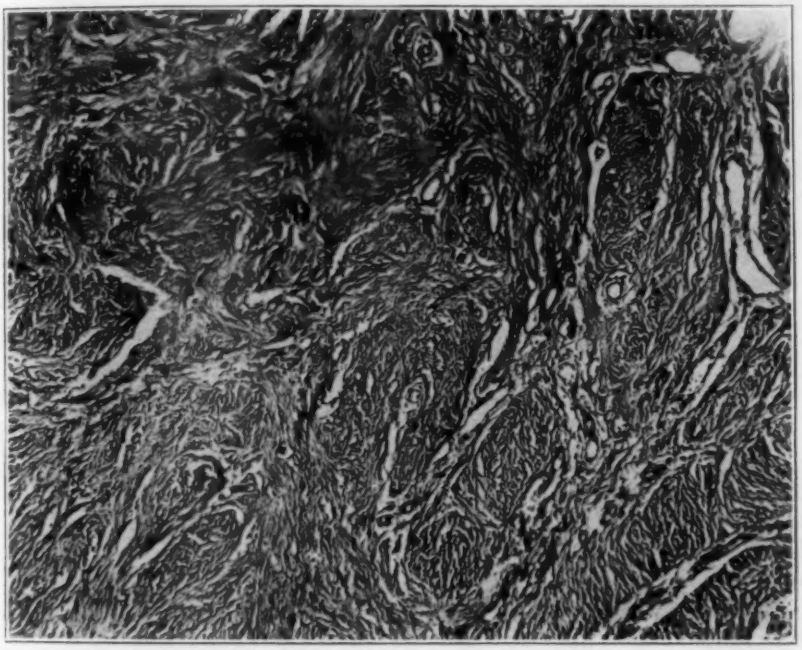

Fig. 11.—Photomicrograph showing a section (× 50) from a hypertrophied scar of the hand, following on a burn one year previously, in a 5 year old white boy. The connective tissue was dense and poorly cellular and showed a pronounced tendency toward whorl formation. Some of the vessels revealed scattered lymphocytes about their periphery—a feature which was prominent in less densely fibrous regions of this specimen.

with the detection of early or even moderate involvement of this fascia, a structure anatomically identical with palmar fascia.

Remarks.—The following conclusions were drawn:

1. The pathologic tissues in this series of 35 cases could not be grouped or graded on the basis of predominance of any distinctive feature or features. In most of the material, wide variation in histologic characteristics was evident within the same specimen.

2. The variable cellularity of the tissues did not appear to indicate accurately the activity of the proliferative process. No constant relation could be ascertained between the histologic picture and such clinical features as the age of the patient, the duration of the pathologic process (as noted by the patient) and the severity and extent of the deformity (figs. 6 and 7).

3. No definite relation could be established between the histologic picture and the likelihood of recurrence, for in the cases in which there was recurrence, the pathologic features were not different from those in cases in which no recurrence was clinically demonstrable (fig. 8).

Fig. 12.—Photomicrograph showing a section (× 45) from a desmoid excised from the wall of the abdomen of a 31 year old woman. The desmoid had appeared at the site of the healed scar of an uncomplicated laparotomy, performed four years previously. In some areas, the tumor is composed of closely compacted poorly cellular connective tissue, while in other regions the tissue is more cellular, well vascularized and loose in texture.

4. The evidence in favor of a chronic inflammatory basis for palmar fibrosis was not striking. The presence of collections of lymphocytic cells was observed in only 13 of the 35 specimens; in some instances their distribution was widespread, while in others it was sparse. When present, these collections bore no definite relation to the clinical features or to other histologic features (fig. 7). Even in those cases in

which tenderness of the thickened palmar fascia and of the involved fingers had been present clinically, inflammatory features were not clearcut. These collections of inflammatory cells had to be carefully differentiated from focal collections of compacted hypercellular tissue immediately adjacent to some of the blood vessels. The significance of these lymphocytic collections is not clear, but it is noteworthy that they were abundantly demonstrable in cases in which there was keloid formation—another example of localized benign fibroplasia (figs. 10 and 11).

5. There was no evidence to substantiate the idea that the proliferative process involving the palmar fascia might originate from the walls of the blood vessels. In some instances, thickening of the vessel wall was noted, and this was interpreted as possibly representing concomitant fibroplasia in the vascular connective tissues or, in the older specimens, a senile degenerative process.

6. In those areas in which fibroblasts were abundant, interlaced and had assumed whorl-like arrangements, the histologic structure was not dissimilar to that of keloid, fascial desmoid and fibroma (figs. 10, 11 and 12).

7. Identical connective tissue hyperplasia may involve plantar fascia (fig. 9).

COMMENT

Most of the theories relating to the causation of Dupuytren's contracture appear to have been founded on wholly inadequate evidence. The importance of such factors as trauma, chronic specific or nonspecific inflammatory processes, circulatory stasis, toxins (focal infections, gout, diabetes mellitus, arthritis), embryologic malformations, peripheral or central neurologic disturbances and endocrinopathies has not been substantiated by a critical analysis of the clinical and histologic material in this investigation and of the data reported by other writers.

Certain other factors, however, do appear to have some significance:

Heredity.—The occurrence of Dupuytren's contracture in several generations in the same family and the high familial incidence in large series of cases have been noted by numerous authors.

Senility.—The contracture occurs most frequently in middle life and in old age. It is not unlikely that this fact may be related, at least in part, to the presence of such degenerative and proliferative processes as were noted in this study in the vascular and connective tissues of normal palmar fascias in patients in the later decades of life.

Fibroblastic Diathesis or Predisposition.—The theory of a constitutional predisposition to connective tissue proliferation has been suggested by some observers because of the concomitant occurrence in some cases

of Dupuytren's contracture of thickening and contracture of the plantar fascias and of induration of the penis. There is a striking histologic resemblance of the fibroblastic process in Dupuytren's contracture to other localized fibroplasias, such as keloid and fascial desmoid. A keloid is a localized overgrowth of hyaline connective tissue developing in the skin of a predisposed person, usually at the site of scarring, although it may arise spontaneously. A desmoid is a fibroma of the abdominal wall. Although the relation of desmoids to trauma (e. g., from gestation) cannot be overlooked, the congenital origin of some and the origin of many others in the scars of uncomplicated laparotomy suggest an anatomic predisposition of the affected tissue to desmoid formation in certain subjects. Furthermore, like Dupuytren's contracture, both keloid and fascial desmoid are prone to recur despite extensive surgical excision.

SUMMARY AND CONCLUSIONS

This study of Dupuytren's contracture embraces: (1) the normal gross anatomy of the human palmar fascia (material: 60 hands); (2) the microscopic anatomy of the palmar fascia in human cadavers presenting no gross abnormality of this structure (material: 27 specimens); (3) the histologic features of Dupuytren's contracture (material: 35 cases).

The deformity in Dupuytren's contracture was found to be intimately related to the gross anatomic structure of the fascial layers and septums of the hand. Widespread surgical excision of these tissues is essential to effect and maintain correction of the deformity.

The tendon-like structure of normal palmar fascia and the proliferative and degenerative changes which occur in this tissue with advancing years may have some bearing on the development of fibrosis of the palmar tissues in Dupuytren's contracture—a condition most prevalent in the later decades of life.

The essential process in Dupuytren's contracture is benign fibroplasia of the palmar connective tissues. Inflammatory features are not constant, nor is there evidence that the proliferative process arises from the walls of blood vessels. The histologic features and the clinical behavior of this fibroblastic process bear a striking resemblance to those of other localized fibroplasias, such as keloid and fascial desmoid.

Such factors as heredity, senility and fibroblastic diathesis or predisposition appear to be of importance in the causation of Dupuytren's contracture.

REFLEX CHANGES IN RESPIRATION INDUCED BY DISTENTION OF THE SMALL INTESTINE

ROBERT T. CROWLEY, M.D.
DETROIT

The importance of distention in the various portions of the gastrointestinal tract has been frequently stressed in experimental and clinical literature. Such interest has arisen largely from repeated demonstrations that the distention inevitably appearing on intestinal obstruction is the factor chiefly responsible for the grave physiologic disturbances associated with that condition.[1] Whether experimentally produced or resulting from actual pathologic conditions, excessive intraluminal pressure in the small intestine has been shown to produce a variety of local and general effects. Among the changes induced locally in the distended bowel segment are alterations in the motility,[2] the circulation,[3] the absorption [4] and the secretion.[5] Changes of a more general character occurring in the entire volume of circulating blood include disturbance of the cell-plasma ratio [6] and fluctuation of the level of nitrogenous substances in the blood.[7] Certain other effects, apparently reflex responses to the stimulus of distention, are much less familiar. Among these is the marked respiratory response elicited by the stimulus of excessive dis-

This study was aided by a grant from the McGregor Foundation.

From the Department of Surgery, Wayne University College of Medicine.

1. (*a*) Herrin, R. C., and Meek, W. J.: Distention as a Factor in Intestinal Obstruction, Arch. Int. Med. **51**:152 (Jan.) 1933. (*b*) Johnston, C. G.: Decompression in the Treatment of Intestinal Obstruction, Surg., Gynec. & Obst. **70**:365, 1940. (*c*) Taylor, N. B.; Weld, C. B., and Harrison, G. K.: Experimental Intestinal Obstruction, Canad. M. A. J. **29**:227, 1933.

2. Röden, S. H.: An Experimental Study of Intestinal Movements, Particularly with Regard to Ileus Conditions in Cases of Trauma and Peritonitis, Acta chir. Scandinav. (supp. 51) **80**:1, 1937. Youmans, W. B.; Meek, W. J., and Herrin, R. C.: Extrinsic and Intrinsic Pathways Concerned with Intestinal Inhibition During Intestinal Distention, Am. J. Physiol. **124**:470, 1938.

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4. Wangensteen, O. H.: The Therapeutic Problem in Bowel Obstructions, Springfield, Ill., Charles C. Thomas, Publisher, 1937, p. 36.

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6. Fine, J.; Fuchs, F., and Gendel, S.: Changes in Plasma Volume Due to Decompression of the Distended Small Intestine, Arch. Surg. **40**:710 (April) 1940.

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tention rapidly induced in the small intestine. A search of the literature has revealed little dealing with this phenomenon. It is the purpose of this communication to present observations obtained in an experimental investigation of this particular effect, namely, the changes produced in the character and the volume of respiration by excessive distention rapidly induced in the small intestine.

PROCEDURES

Dogs were the experimental animals employed; 30 were used in the course of the experiments. With the animal under anesthesia produced by intravenous and intraperitoneal injections of soluble pentobarbital (30 mg. per kilogram of body weight), a cannula was placed in the right carotid artery and a pleural cannula inserted in the chest. The blood pressure was recorded on a kymograph with a

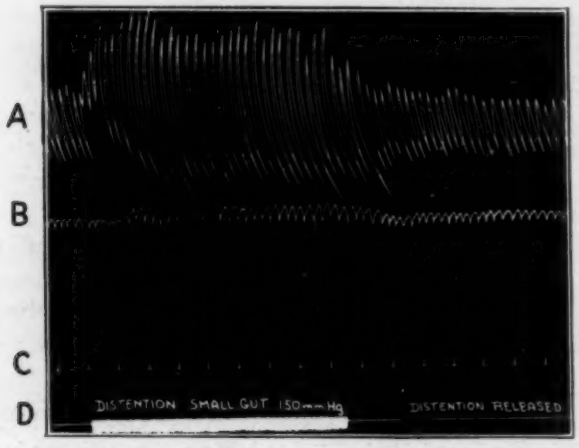

Fig. 1.—Typical alterations in the respiration and the blood pressure obtained on distention of a segment of the ileum 2 feet (61 cm.) from the ileocecal valve. The dog weighed 12.5 Kg. Anesthesia was induced by the intravenous injection of 30 mg. per kilogram of body weight of soluble pentobarbital. *A*, respiration; *B*, blood pressure; *C*, time units at intervals of six seconds and at a blood pressure level of zero; *D*, signal.

mercury manometer, and the respiratory tracing was obtained simultaneously by means of a tambour. The abdomen was opened through a midline incision, and the distending tube, fashioned from a Foley catheter, was inserted into the lumen of the intestine through an incision in the bowel wall at the antimesenteric border perpendicular to the long axis To prevent possible slipping of the tube from its position in the lumen, two sutures were passed through the tube and the entire thickness of the intestine; thus it was secured firmly in place. Distention of the intestine was performed at intervals by injecting varying quantities of air from a 50 cc. syringe into the inflation cuff of the catheter lying in the lumen. The intraluminal pressure was measured by means of a mercury manometer interposed between the distending tube and the syringe used for the injection of air.

Numerous readings during control periods without distention were taken for all animals. Distention of the tube was carried out with the segment of the bowel outside the abdominal cavity covered with cloths moistened with warm 0.9 per cent solution of sodium chloride. Various procedures were then undertaken to learn the effect which they might produce on the respiratory changes elicited by distention. These procedures included unilateral and bilateral vagotomy, bilateral adrenalectomy, section of the spinal cord at the level of the second thoracic vertebra,

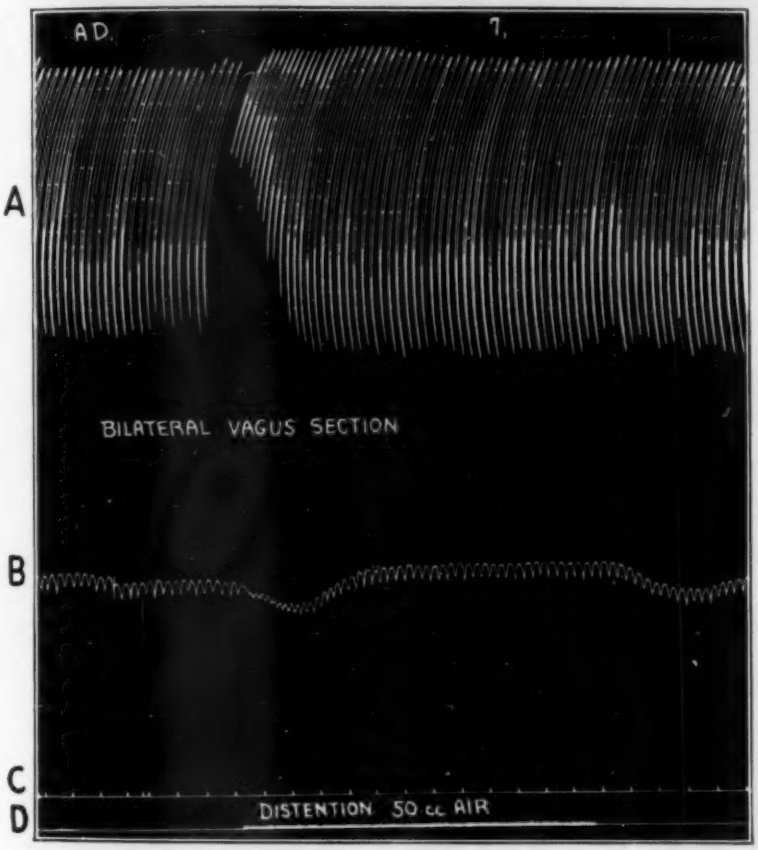

Fig. 2.—Persistence of the respiratory and the blood pressure changes occurring on distention of an isolated loop of the jejunum with an intact mesentery after previous bilateral adrenalectomy and bilateral vagotomy. The dog weighed 17 Kg. Anesthesia was induced by the intravenous injection of 30 mg. per kilogram of body weight of soluble pentobarbital.

section of the splanchnic nerves to the bowel segment, cocainization of the splanchnic nerves to the bowel segment and the intravenous administration of atropine sulfate (6 mg. per kilogram of body weight) and of ethyl yohimbine (5 mg. per kilogram of body weight). The effect of employing the faradic current to stimulate the splanchnic nerves of the undistended segment of the intestine, in which the dis-

tending tube was placed, also was observed. To elucidate more clearly the effect of the distention stimulus on respiration before and after the procedures just described, the observations made will be detailed in conjunction with typical kymographic tracings in each instance.

OBSERVATIONS

1. Distention of various segments of the small intestine from the duodenum to the ileocecal valve invariably produced a marked respiratory

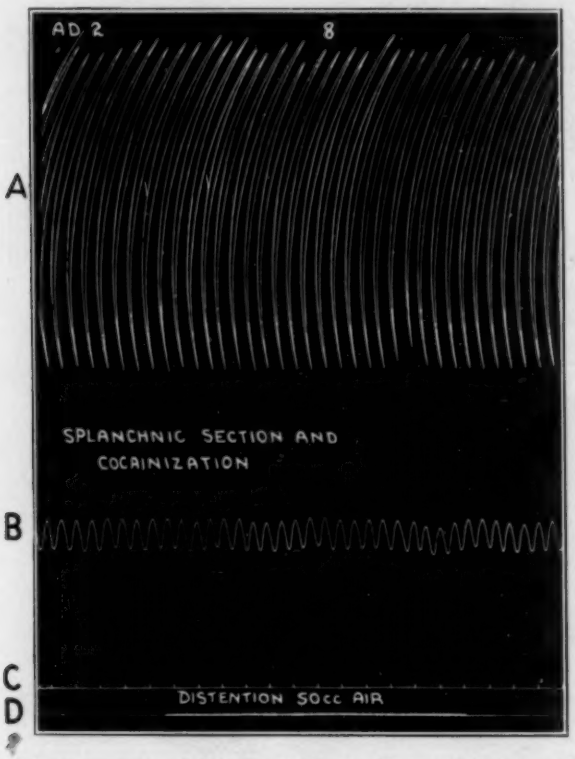

Fig. 3.—Disappearance of the respiratory effects elicited by distention of a loop of the ileum after section and cocainization of the splanchnic nerve fibers to the distended bowel segment. The dog weighed 18.5 Kg. Anesthesia was induced by the intravenous injection of 30 mg. per kilogram of body weight of soluble pentobarbital.

change. This change consisted of an arrest in the respiratory rhythm, usually in the expiratory phase, sometimes of apnea, for a period, followed immediately by an increased respiratory volume, which persisted as long as the distention of the intestine was maintained. On release of the distention, respiration promptly returned to the previous normal

state. Coincident with the change observed in respiration on distention of the intestine, there was invariably marked fluctuation of the blood pressure. This consisted of an initial drop in the pulse pressure, usually accompanied by a fall of the blood pressure level, immediately succeeded by a marked elevation of the pressure level, which was maintained as long as the bowel remained distended; on deflation the blood pressure returned to approximately the normal level (fig. 1). Both the respiratory

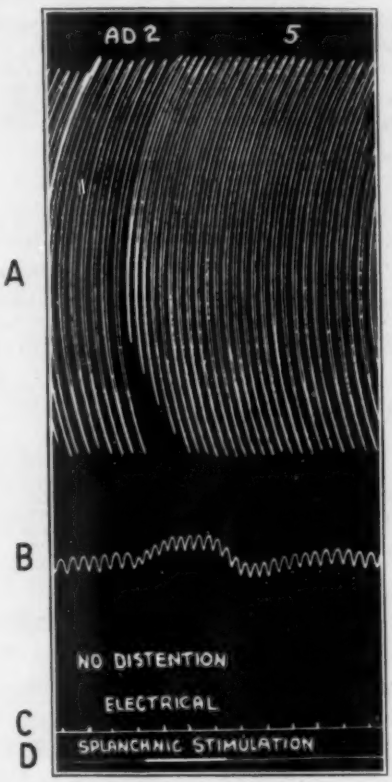

Fig. 4.—Similarity between the respiratory and the blood pressure effects obtained by electric stimulation of the splanchnic nerve fibers in the undistended bowel segment and those elicited by distention. The dog weighed 18.5 Kg. Anesthesia was induced by the intravenous administration of 30 mg. per kilogram of body weight of soluble pentobarbital.

and the blood pressure effects were roughly in direct proportion to the amount of distention induced—the greater the distention, the more accentuated the respiratory and circulatory changes. Likewise, both the respiratory and the blood pressure changes attending distention varied

inversely with the depth of the narcosis; they were appreciably less when a greater dose of the anesthetic drug was administered, although they never disappeared entirely.

2. Unilateral and bilateral section of the vagi in the neck were performed before distention and exerted no effect on the characteristic changes occurring on subsequent distention of the bowel segment (fig. 2).

3. Bilateral adrenalectomy performed on animals one hour before distention failed to show any influence whatever on the respiratory and the blood pressure changes elicited by subsequent periods of distention (fig. 2).

4. When the segment of the intestine to be distended was entirely separated from the rest of the bowel with its mesenteric connections left intact (formation of an isolated loop), distention in that segment

Experiments with Respect to the Effect of Distention of the Small Intestine

Procedure	Dogs	Result
Distention only	30	Marked respiratory and blood pressure changes
Distention after vagotomy	12	Marked respiratory and blood pressure changes
Distention after adrenalectomy	2	Marked respiratory and blood pressure changes
Distention in an isolated loop of the intestine	6	Marked repiratory and blood pressure changes
Distention after the administration of atropine sulfate	6	Marked respiratory and blood pressure changes
Distention after the administration of ethyl yohimbine	2	Marked respiratory and blood pressure changes
Distention after section of the spinal cord	4	No effect on respiration or blood pressure
Distention after section and cocainization of the splanchnic radicals	2	No effect on respiration or blood pressure
Faradic stimulation of the splanchnic radicals	2	Marked respiratory and blood pressure changes, similar to, if not identical with, those obtained by distention

produced the same characteristic changes in respiration and blood pressure as before (fig. 2).

5. The intravenous administration of either atropine sulfate (6 mg. per kilogram of body weight) and/or ethyl yohimbine (5 mg. per kilogram of body weight) exerted no influence on the effect produced by the distention stimulus after intervals of one-half, one and two hours.

6. Section of the spinal cord at the level of the second thoracic vertebra in animals previously prepared completely eliminated both the respiratory and the blood pressure changes produced by distention.

7. The respiratory and the blood pressure effects also were entirely absent when distention was produced after isolation and transection of the splanchnic nerve radicals to the bowel segment in which the distending tube was placed. Cocainization of these splanchnic radicals with 2 per cent solution of cocaine produced the same effect as section of the fibers (fig. 3). The use of the faradic current to stimulate the intact fibers of the splanchnic radicals to the undistended segment produced

changes in the respiration and the blood pressure strikingly similar, if not identical, with those obtained with the stimulus of distention (fig. 4).

With regard to the preceding observations, it should be stated that the results obtained under the conditions described were the same in all employed for confirmation. The table briefly summarizes these observations.

COMMENT

These observations indicate that the variation in the respiration and the blood pressure observed after distention of the various parts of the small intestine are a definite physiologic response to the distention stimulus. That this phenomenon is of a reflex character cannot be doubted. It is well known that mechanical stimulation of the viscera produces marked reflex changes in the respiration and the blood pressure of completely anesthetized animals. Attention has been drawn also to the fact that the specific stimulus of distention is capable of producing marked respiratory and blood pressure changes when applied to such hollow viscera as the gallbladder and the rectum. The reflex respiratory changes elicited by distention of the small intestine have apparently received but little consideration. In 1928, Schrager and associates [8] showed that excessive distention of the biliary passageways greatly influenced the character of the respirations in experimental animals. In this work clinical examples also were set forth to show that the changes produced by distention of the biliary passages were sufficiently marked to be used as a diagnostic criterion. Moreover, these investigators also noted that distention of the stomach and the jejunum produced some inhibition of respiration which was followed by an increase, although not as marked as that appearing on distention of the biliary passages.

Postulating that the same responses are elicited by distention of the small intestine of the human subject as have been demonstrated in the dog, it does not seem unreasonable to assume that respiration may be considerably modified by the presence of conditions in which excessive distention of the small intestine occurs.

Whatever clinical significance may be attached to the respiratory and the blood pressure changes associated with distention of the small intestine, the present observations are primarily concerned with their physiologic aspects. From these observations it appears that the phenomenon is entirely consistent in its appearance although individual quantitative variations do occur. It is not apparently a specific reaction to the distention stimulus alone, since stimulation of the splanchnic radicals to the undistended bowel segment by other means (faradic current) elicits a similar response. It also appears that the afferent

8. Schrager, V. S., and Ivy, A. C.: Symptoms Produced by Distention of the Gallbladder and Biliary Ducts, Surg., Gynec. & Obst. **47**:1, 1928.

impulses set up by the distention stimulus travel by way of the visceral afferent fibers in the splanchnic radicals to the distended bowel segment and not by way of the vagal ramifications, since the respiratory and the blood pressure effects persist unaltered after vagal section and disappear when the splanchnic radicals are cut or cocainized. That these visceral afferent fibers run more or less directly from the bowel into the mesentery and do not pass for any length in the bowel wall before entering the mesentery is demonstrated by the persistence of the effect on respiration in isolated loops. It is interesting to note in this connection that distention of a portion of the intestine about 2 inches (5 cm.) in length will produce the effect. It is obvious that some part of the nervous pathway, either afferent or efferent, producing the effect lies in the spinal cord from the fact that section of that structure at the level of the first or the second thoracic vertebra completely abolishes the respiratory changes. The fact that atropine sulfate and ethyl yohimbine in doses sufficient to remove parasympathetic and sympathetic action do not eliminate the respiratory changes occurring on distention indicates that the anatomic efferents, both cholinergic and adrenergic, are only slightly if at all involved.

SUMMARY

Marked respiratory changes, reflex in character, invariably follow excessive distention rapidly induced at any level of the small intestine of the anesthetized dog. These changes are of a characteristic pattern and are accompanied by synchronous fluctuations in the blood pressure. They are apparently initiated by afferent impulses arising from the stimulus of distention and mediated by fibers of the splanchnic nerve radicals to the distended bowel segment and subsequently by pathways in the spinal cord, since they are eliminated by complete section of either of these structures.

The vagus nerves and the adrenal glands are not involved in the production of the respiratory and the blood pressure effects since these continue to appear after transection of the former and total extirpation of the latter.

Drugs inhibiting the action of the efferent components of the autonomic nervous system, both adrenergic and cholinergic, exert little or no action on the respiratory alteration appearing on distention. Drugs depressing the visceral afferent impulses from the distended bowel segment lessen the respiratory and blood pressure phenomena and, if given in sufficient doses, abolish them entirely.

Drs. Charles G. Johnston and Frederick Yonkman gave assistance and advice throughout the experiment.

CARCINOMA OF THE FEMALE BREAST

AN ANALYSIS OF THE END RESULTS AFTER FIVE YEARS IN ONE HUNDRED AND NINETY-TWO CASES, WITH SPECIAL CONSIDERATION OF PREOPERATIVE IRRADIATION

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In an earlier article [1] I published the data on 192 cases of primary and recurrent carcinoma of the female breast occurring during the period from Jan. 1, 1931 to Dec. 31, 1935. Patients observed during this time were selected for study because this period marked the beginning of my experience with preoperative irradiation for operable carcinoma of the breast. In table 1 (reproduced from my earlier article) the classification of patients according to method of treatment

TABLE 1.—*Classification of Patients According to Treatment and Results*

Group	Status	No. of Patients
1	Preoperative irradiation and complete operation	43
2	Complete operation; no preoperative irradiation	51
3	Irradiation only, including excision of tumor and biopsy	42
4	Excision of breast only	9
5	Recurrent carcinoma	41
6	Insufficient record	6
	Total	192

applied for the eradication of primary tumor is given. The cases of recurrent carcinoma are included but are separately considered.

The analysis of these 192 cases and the study of the results to September 1936 seemed to indicate that the routine employment of preoperative irradiation might have value as an adjunct to the complete operation in the treatment of operable carcinoma of the female breast. In making microscopic studies I found no residual carcinoma in the breast or the axillary lymph nodes in 10 (24 per cent) of the 43 cases in which preoperative irradiation and the complete operation were done (group 1), although preoperative biopsy showed that the disease was present in 7 instances. Seventy-one per cent of the patients who were given this combined treatment were living and free from recurrence for an average of one year and ten months after the beginning of irradiation, while only 33 per cent of the 51 patients treated by the

1. Cohn, L. C.: Carcinoma of Female Breast, with Special Consideration of Preoperative Irradiation, Arch. Surg. **35**:694-711 (Oct.) 1937.

complete operation without preoperative irradiation (group 2) were living and without clinical evidence of recurrence. In this group, however, an average of three years and four months, almost double the time in group 1, had elapsed since operation. Even after finding that carcinoma in the breast could be completely eradicated by irradiation therapy in almost 1 of 4 instances and after learning that more than twice as many patients survived after the combined treatment than after treatment by operation alone, I made the following statement with reference to the value of preoperative irradiation: "The solution of

TABLE 2.—*End Results for Patients in Group 1* *

Total number of patients				43
Dead postoperatively from infection				1
Patients available for consideration of the ultimate result				42
	1936	1938	1941	
Living, free from recurrence	30 (71%)	28 (51%)	21 (50%)	
Average time since operation, 6 years				
Living, with recurrence	4	1		
Dead from cancer	15 (28%)	19 (44%)	21 (50%)	
Average time since operation, 2 yr. 6 mo.				
Under five years			18	
Over five years			3	
Five year cures				24 (57%)

* In this and the following tables the end results are computed for a period ending Feb. 1, 1941.

TABLE 3.—*End Results for Patients in Group 2*

Total number of patients				51
	1936	1938	1941	
Living, free from recurrence	17 (38%)	13 (26%)	10 (19.6%)	
Average time since operation, 7 yr. 6 mo.				
Living, with recurrence	3	2		
Dead from cancer	28 (60%)	34 (70%)	41 (80.4%)	
Average time since operation, 2 yr. 11 mo.				
Under five years			33	
Over five years			8	
Five year cures				18 (35%)

this problem, at least as far as this series of patients is concerned, will have to await the passage of time."

It is now more than five years since treatment was carried out in this series of cases, and I wish to present the accumulated evidence for and against the value of preoperative irradiation. The end results for the patients in group 1 are summarized in table 2, and the end results for the patients in group 2 are summarized in table 3. In these and the following tables patients remaining free from demonstrable evidence of recurrence or metastases for five years are classified as five year cures, even though they subsequently died of cancer.

Presumptive evidence in favor of the value of preoperative irradiation therapy as a part of the treatment for operable cancer of the breast is derived from a comparison of the gross figures for five year cures in groups 1 and 2. These figures are given in tables 2 and 3 as 57 and 35 per cent, respectively. For the purpose of analysis these figures

have been broken down and studied in relation to the presence or absence and the extent of regional metastasis and in relation to the grade of tumor. The figures in tables 4 and 5 indicate that in group 1 the axillary lymph nodes were free of metastasis in 56 per cent of the

TABLE 4.—*End Results in Relation to Regional Metastasis for Patients in Group 1*

Total number of patients			43
Patients with axillary lymph nodes not involved by metastasis			23 (56%)
Dead under five years from a cause other than cancer			1
Available for consideration of the ultimate result			22
Living and free from recurrence			18 (82%)
Average time since operation, 6 yr. 2 mo.			
Dead from cancer			4
Under five years	3		
Over five years	1		
Five year cures			19 (86%)
Axillary lymph nodes involved by metastasis			18 (42%)
Living and free from recurrence			1 (5.6%)
Dead from cancer			17
Under five years	15		
Over five years	2		
Five year cures			3 (17%)*
No note on involvement of lymph nodes			2

* One patient living with metastasis.

TABLE 5.—*End Results in Relation to Regional Metastasis for Patients in Group 2*

Total number of patients			51
Patients with axillary lymph nodes not involved by metastasis			14 (30%)
Dead under five years from a cause other than cancer			1
Available for consideration of the ultimate result			13
Living and free from recurrence			5 (38%)
Average time since operation, 7 yr. 9 mo.			
Dead			9
From cancer	6		
Under five years	2		
Over five years	4		
From cause other than cancer	3		
Under five years	1		
Over five years	2		
Five year cures			11 (85%)*
Patients with axillary lymph nodes involved by metastasis			33 (70%)
Living and free from recurrence		4 (12%)	
Average time since operation, 6 yr. 6½ mo.			
Dead from cancer	29		
Under five years	27		
Over five years	2		
Five year cures			6 (18%)
Patients with no note on involvement of lymph nodes			4

* One patient living with carcinoma of the pancreas.

cases, while in group 2 such was the case in only 30 per cent. It seems important to determine, and yet at the present time it is obscure, whether this variation in the percentage of regional metastasis in the two groups was due to the exposure of the lymph nodes of the patients in group 1 to irradiation. It seems significant that when the axillary lymph nodes were not involved by metastasis, the percentages of patients in the two groups remaining free of clinical evidence of the

disease for five years were almost identical—86 in group 1 and 85 in group 2. When the axillary lymph nodes were involved by metastasis, the five year cures were 17 per cent in group 1 and 18 per cent in group 2. These figures seem to indicate that the percentage of five year survivals is to a large extent determined by the presence or the absence of regional metastasis at the time of operation.

TABLE 6.—*End Results in Relation to the Extent of Regional Metastasis for Patients in Group 1*

Total number of patients			43
Patients with axillary lymph nodes involved by metastasis		18 (42%)	
Patients with metastasis to basal axillary glands only	6		
Living and free from recurrence	1		
Dead from cancer	5		
Under five years	4		
Over five years	1		
Five year cures		2 (33%)	
Patients with metastasis to basal and middle axillary glands	1		
Dead from cancer under five years	1		
Five year cures	0		
Patients with metastasis to basal, middle and highest apical axillary glands	7		
Dead from cancer under five years	7		
Five year cures	0		
No note on the extent of regional metastasis		4	

TABLE 7.—*End Results in Relation to the Extent of Regional Metastasis for Patients in Group 2*

Total number of patients			51
Patients with axillary lymph nodes involved by metastasis		33 (70%)	
Patients with metastasis to basal axillary glands only	7		
Living and free from recurrence	0		
Dead from cancer	7		
Under five years	6		
Over five years	1		
Five year cures		1 (14%)	
Patients with metastasis to basal and middle axillary glands	6		
Living and free from recurrence	2		
Dead from cancer under five years	4		
Five year cures		2 (33%)	
Patients with metastasis to basal, middle and highest apical axillary glands	12		
Living and free from recurrence	1		
Dead from cancer under five years	11		
Five year cures		1 (8%)	
No note on the extent of regional metastasis		8	

The end results in relation to the extent of involvement of the axillary lymph nodes are summarized in tables 6 and 7. The total of cases in each subgroup is too small for comparative study; yet the figures seem to indicate that even when there is extensive involvement of the axillary lymph nodes, the use of preoperative irradiation does not contribute toward increase in the number of five year cures.

The end results in relation to the grade of tumor are summarized in tables 8 and 9. In group 1 the actual and relative numbers of grade 1 tumors were far greater than in group 2; thus a basis for comparison

is lacking. However, reports in the literature and personal experiences convince me that five year cures approaching 90 per cent can be expected from treatment entirely by operation for patients harboring grade 1 tumor.

TABLE 8.—*End Results in Relation to Grade of Tumor for Patients in Group 1*

Total number of patients			43
Patients with grade 1 tumor			8
Living and free from recurrence		7 (90%)	
Average time since operation, 5 yr. 10 mo.			
Dead from cancer under five years		1	
Patients with grade 2 tumor			12
Living and free from recurrence		6	
Average time since operation, 7 yr.			
Dead from cancer		6	
Average time since operation, 2 yr. 6 mo.			
Under five years	4		
Over five years	2		
Five year cures		8 (66%)	
Patients with grade 3 tumor			18
Living and free from recurrence		4	
Average time since operation, 6 yr.			
Dead from cancer		14	
Under five years	13		
Over five years	1		
Five year cures		5 (28%)	
Patients with grade 4 tumor			2
Well five years		1	
Dead from a cause other than cancer		1	
Patients with unclassified tumor			3

TABLE 9.—*End Results in Relation to Grade of Tumor for Patients in Group 2*

Total number of patients			51
Patients with grade 1 tumor			2
Living and free from recurrence		0	
Patients with grade 2 tumor			15
Living and free from recurrence		6	
Average time since operation, 7 yr. 5 mo.			
Dead		9	
From cancer		7	
Average time since operation, 4 yr. 2 mo.			
Under five years	4		
Over five years	3		
From a cause other than cancer		2	
Under five years	1		
Over five years	1		
Five year cures		10 (66%)	
Patients with grade 3 tumor			29
Living and free from recurrence		4	
Average time since operation, 7 yr.			
Dead from cancer		25	
Under five years	21		
Over five years	4		
Five year cures		8 (27.5%)	
Patients with grade 4 tumor			2
Dead from cancer		2	
Patients with unclassified tumor			3

When the histologic picture of the tumor corresponded to grade 2, 66 per cent five year cures were obtained whether or not preoperative irradiation was used in conjunction with the operation. When the tumor was grade 3 from the histologic appearance, approximately 28

per cent five year cures resulted from treatment by either method. Four tumors because of their extreme anaplastic structure were placed in grade 4. Two of these tumors were in group 1 and two in group 2. The only five year cure was in group 1.

Group 3 consisted of 42 women with carcinoma of the breast treated by irradiation with roentgen rays or by a combination of roentgen rays and radium but not subjected to the complete operation (table 10). Thirty-eight of these were considered suitable for consideration of the

TABLE 10.—*End Results for Patients in Group 3*

Gross End Results			
Total number of patients			42
Lost from observation			3
Patients remaining for consideration of the gross end results			39
Living and free from recurrence		4 (10%)	
Average time since the beginning of irradiation, 7 yr. 9 mo.			
Dead		35	
From a cause other than cancer	2		
Under five years	1		
Over five years	1		
From cancer	33		
Average duration of life since the beginning of irradiation, 1 yr. 6 mo.			
Under five years	32		
Over five years (patient subjected to complete operation for recurrence)	1		
Five year cures		6 (16%)	
End Results in Relation to Operability of Tumor			
Total number of patients			42
Lost from observation			3
Patient subjected to complete operation after recurrence			1
Patients remaining for consideration of end results			38
A. Patients with inoperable tumor		27	
Living more than five years		1	
Dead from cancer under five years		26	
Five year cures		1 (4%)	
B. Patients with operable tumor		11	
Living and free from recurrence		3	
Dead		8	
From a cause other than cancer	2		
Under five years	1		
Over five years	1		
From cancer	6		
Under five years	6		
Five year cures		4 (36%)	

end results. The gross five year cures in this group were 16 per cent. Twenty-seven tumors (70 per cent) were considered inoperable because of the extent of the local and regional involvement or because of the presence of distant metastasis when the patient was first examined (*A*, table 10). Twenty-six of these patients died from cancer within five years, and only 1 (4 per cent) is still alive at the time of writing. There were 11 patients with operable tumor on whom it would have been feasible to perform the complete operation, but for various reasons the operation was restricted to biopsy or to excision of the tumor in 8 cases. There was no biopsy in 3 cases. The breast, the axilla and the supraclavicular area of each patient were treated by irradiation. The five year cures in this group were 36 per cent. In each of the 3

instances in which the patient is living and free from evidence of recurrence for more than five years at the time of writing, the tumor had been excised and considered on microscopic study to be low grade. Two of these tumors were colloid carcinoma; the other was adenocarcinoma of the sweat gland type. One patient died more than five years after irradiation therapy from a cause other than cancer. When first examined she was 76 years of age and had been aware of the presence of the tumor of the breast for one month. This tumor, which was clinically malignant, rapidly disappeared under irradiation therapy. However, there was no biopsy to confirm the clinical diagnosis of cancer.

The end results in group 4 are given in table 11. This group comprised those patients whose breast was excised by a restricted

TABLE 11.—*End Results for Patients in Group 4*

Total number of patients			9
Patients given preoperative irradiation			4
Dead from cancer under five years		1	
Living and free from recurrence		3 (75%)	
Patients given no irradiation			5
Dead		4	
From cancer under five years	3		
From a cause other than cancer under five years	1		
Living and free from recurrence		1 (25%)	
Five year cures		4 (50%)	

TABLE 12.—*End Results for Patients in Group 5*

Total number of patients			41
Dead under five years for a cause other than cancer			1
Patients remaining for consideration of the end result			40
Living and free from recurrence		0	
Dead from cancer		40	
Average duration of life after first examination, 1 yr. 4½ mo.			
Five year cures		0	

operation, the extent of which did not conform to the standards set for the complete operation. In all but 1 instance the extent of the operation exceeded that of simple mastectomy and consisted of the excision of the breast and the pectoral muscles or the excision of the breast and the axillary lymph nodes but not of the pectoral muscles. The gross five year cures in this group were 50 per cent. The number of cases are too few and the operations too unlike for comparison. Three of the 4 patients (75 per cent) receiving preoperative irradiation are living and free from recurrence for more than five years after operation at the time of writing. The tumor in 1 instance was comedo-adenocarcinoma and in 2 cases grade 2 scirrhous carcinoma. One of the 5 patients, whose treatment was entirely surgical, died under five years from a cause other than cancer. Three died from cancer. One (25 per cent) is living and free from recurrence at the time of writing. This tumor was grade 3 scirrhous carcinoma.

SUMMARY AND CONCLUSIONS

The five year cures among 94 patients with carcinoma of the breast subjected to the complete operation are calculated to be 45 per cent (table 13). In 51 of these cases the treatment was entirely surgical, and the five year cures in this group were 35 per cent. In 43 cases, preoperative irradiation was used in conjunction with the surgical treatment, and the five year cures were 57 per cent. Analysis seems to indicate that the end results have been largely determined by the grade of the tumor and the condition of the axillary lymph nodes at the time of operation. From the study of my material I am unable to state whether or not the condition of the axillary lymph nodes and the grade of the tumor were modified when preoperative irradiation was

TABLE 13.—*Gross Five Year Cures*

Groups 1 and 2		
Total number of patients		94
Postoperative death from infection	1	
Patients available for consideration of the ultimate result	93	
Five year cures	42 (45%)	
Groups 3B and 4		
Total number of patients		20
Death from a cause other than cancer under five years	1	
Patients available for consideration of the ultimate result	19	
Five year cures	8 (42%)	
Group 3A and 5		
Total number of patients		68
Death from a cause other than cancer under five years	1	
Patients available for consideration of the ultimate result	67	
Five year cures	1 (<1%)	

used. The solution of this problem would certainly permit a more accurate estimate of the value of preoperative irradiation.

The five year cures in a group of 20 operable patients not subjected to the complete operation are calculated to be 42 per cent. The survivors are composed of patients treated by simple excision of the tumor followed by irradiation therapy or by amputation of the breast in a restricted operation. The majority of the latter received preoperative irradiation. The relatively large number of survivors seems to have been greatly influenced by the presence in this group of a large percentage of low grade tumors, and there is also some evidence that irradiation therapy has influenced the end results.

The five year cures in 68 cases of inoperable and recurrent carcinoma of the breast are calculated to be less than 1 per cent. Analysis reveals no actual evidence that the end results have been materially modified by the use of irradiation therapy in 67 of the cases.

SARCOMA OF THE BREAST

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The development of knowledge of sarcoma of the breast has been handicapped by confusion in classification, a state still prevalent to some extent. This has been due chiefly to the striking variability of the manifestations of sarcoma of the breast (in contrast to the uniformity exhibited by sarcoma in other regions) and to the infrequency of its occurrence—factors all too apparent in any review of the subject in which there is an attempt to place the various forms in well defined groups.

The older literature contains numerous examples of so-called breast sarcoma classified with little regard to histogenesis and subsequent course but largely on gross or microscopic appearance. The prevailing tendency was to name the neoplasms according to the morphologic characteristics of the component elements; the result was the development of a multitude of terms, most of which convey little information as to the tissue of origin. Therefore, although one can speculate, it is difficult and often impossible to be certain of exactly what such tumors were. It also seems unquestioned that in the past the term "sarcoma" has been used loosely as a convenient category for those neoplasms that were not frankly epithelial in nature. Thus, there has been a steady decline in the reputed frequency as more and more atypical forms of carcinoma, benign tumors and the like have been excluded from the general group. Today the incidence is given as between 0.5 and 3 per cent of all malignant breast tumors [1] in contrast to an incidence of 6 to 9 per cent in the earlier

From the Surgical Pathology Laboratory of the Columbia University College of Physicians and Surgeons and the Department of Surgery of the Presbyterian Hospital and Sloane Hospital for Women.

1. Boldrey, E. B.: Primary Sarcoma of the Breast, with Report of Four Cases, Canad. M. A. J. **35**:16, 1936. Fox, S. L.: Sarcoma of the Breast: Report of Sixty Cases, Ann. Surg. **100**:401, 1934. Pack, G. T., and LeFevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, J. Cancer Research **14**:167, 1930. Rose, J.: Die Sarkome der weiblichen und die Geschwülste der männlichen Brustdrüsen nach dem Material der chirurgischen Klinik zu Leipzig, Deutsche Ztschr. f. Chir.

(Footnote continued on next page)

reports. The latter figures, however, can be reduced to 5 or 6 per cent if instances of cystosarcoma are eliminated. One of the important reasons for this decrease has been the greater realization in recent years of the degree to which cancer cells can assume a spindle shape, and it is now known that such an appearance alone does not necessarily imply sarcoma. Likewise, an alveolar arrangement should suggest at once that the primary change is epithelial in type. It also seems probable that many of the neoplasms formerly designated as round cell sarcoma, perithelioma, cylindroma and angiosarcoma are really carcinoma.

An interesting group of breast neoplasms often incorporated with the sarcoma group was first isolated by Müller in 1838.[2] He recognized their benign clinical course and described three varieties to which he gave the names of simple cystosarcoma, cystosarcoma proliferum and cystosarcoma phyllodes. Two years later, Brodie [3] discussed this same group and mentioned five different stages in the evolution of the tumors. It is likely that Müller's three varieties represented various stages in the development of the same type of neoplasm, a view considered probable by Delbet.[4] Other writers also recognized this particular tumor type and described it under different names; all more or less realized the usually innocent nature of the disease. In 1931, Lee and Pack [5] found 105 examples of this type of tumor in the literature and added 6 more. They recommended the term "giant intracanalicular fibro-adenomyxoma" for it and discussed its characteristics in detail.

One of the first great attempts to segregate the varieties of mammary sarcoma into an organized classification was that of Gross in 1887.[6] He collected 156 cases in all, including 19 of his own. Although he divided sarcoma into three principal forms (spindle, round and giant cell), he had fourteen subvarieties. The differentiation was based largely on morphologic grounds, and for present day purposes this work is of little value except for consideration of the group as a whole.

246:151, 1936. Sailer, S.: Sarcoma of the Breast, Am. J. Cancer **31**:183, 1937. Schreiner, B. F., and Thibaudeau, M. B.: Sarcoma of the Breast, Ann. Surg. **95**:433, 1932. Smith, G. Van S., and Bartlett, M. K.: Malignant Tumors of the Female Breast, Surg., Gynec. & Obst. **48**:314, 1929.

2. Müller, J.: Ueber den feinern Bau und die Formen der krankhaften Geschwülste, Berlin, G. Reimer, 1838, p. 56.

3. Brodie, B. M.: Lectures on Sero-Cystic Tumours of the Breast, London M. Gaz. **25**:808, 1840; reprinted, M. Classics **2**:941, 1938.

4. Delbet, P.: Tumeurs de la mamelle, in Duplay, S., and Reclus, P.: Traité de chirurgie, ed. 2, Paris, Masson & Cie, 1897, vol. 5, pp. 875-906.

5. Lee, B. J., and Pack, G. T.: Giant Intracanalicular Myxoma of the Breast, Ann. Surg. **93**:250, 1931; Giant Intracanalicular Fibro-Adenomyxoma of the Breast: The So-Called Cystosarcoma Phyllodes Mammae of Johannes Müller, Am. J. Cancer **15**:2583, 1931.

6. Gross, S. W.: Sarcoma of the Female Breast, Am. J. M. Sc. **94**:2, 1887.

In 1894, Williams,[7] from a collection of 1,091 cases of sarcoma, found 99 involving the breast. Thirty of these cases formed the basis for his observations, and he divided them into cases of pure sarcoma and cases of adenosarcoma. In 1915, Geist and Wilensky[8] reviewed the subject and going as far back in the literature as 1858 found 423 cases of breast sarcoma. In the final tabulation of these cases, twenty different forms were listed. At the same time, they added 22 examples which they classified as spindle cell sarcoma, round cell sarcoma, giant cell sarcoma, cystosarcoma, fibrosarcoma and perithelioma.

There were many other contributions on this subject during the latter part of the nineteenth and the first part of the twentieth century, but in most of them the classifications were more descriptive than practical. Although these reports have been reviewed, the information contained in them is usually too equivocal to be used in an analysis of these neoplasms.

In the past mammary sarcoma has been divided rather arbitrarily into adenosarcoma and pure sarcoma, and for this study a somewhat similar separation has been maintained. The latter group, however, can be separated into several specific types. Accordingly we have made the following classification:

1. Adenofibrosarcoma (cystosarcoma phyllodes)
2. Fibrosarcoma
3. Lymphoblastoma
4. Malignant hemangioendothelioma
5. Liposarcoma and myosarcoma
6. Mixed tumor

During the years between 1911 and 1940, inclusive, 15 cases of adenosarcoma, 5 of fibrosarcoma, 2 of lymphosarcoma, 2 of leukemic tumor, 2 of carcinosarcoma (?) and 2 of malignant hemangioendothelioma of the mammary gland have been recorded in the Surgical Pathology Laboratory of Columbia University College of Physicians and Surgeons. In this same period there have been 1,990 cases of carcinoma. Thus sarcoma is represented in 1.2 per cent of all malignant mammary tumors without incorporation of the leukemias. If adenosarcoma is eliminated from the malignant class, true sarcoma forms only 0.4 per cent of malignant mammary growths. All of these mammary tumors appeared in females.

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7. Williams, W. R.: Diseases of the Breast, London, John Bale & Sons, 1894, p. 417.

8. Geist, S. H., and Wilensky, A. O.: Sarcoma of the Breast, Ann. Surg. **62**:11, 1915.

ADENOFIBROSARCOMA

The term "adenofibrosarcoma" has been retained because through usage it has become associated with a specific tumor type, but we realize that the epithelial elements play only a passive part in the neoplastic process. Further, the usual benign course of the disease is recognized, and it is questionable if this type of tumor should be called sarcoma at all. However, its sometimes close association with fibrosarcoma and its frequent incorporation in the general group have seemed sufficient justification for its inclusion.

Adenofibrosarcoma develops in two principal ways. In the first, a sarcomatous change takes place in a pericanalicular fibroadenoma with the production of the tumor type often designated as adenosarcoma or adenofibrosarcoma. In the second, the change occurs in an intracanalicular fibroadenoma and constitutes the form commonly called cystosarcoma phyllodes or cystosarcoma. The latter form sometimes reaches an enormous size; this is exemplified in the frequently quoted case of Velpeau in which the tumor attained a weight of 20 Kg.

Adenofibrosarcoma appears most frequently during the fifth decade, but it may be found during any period of life following puberty. It accounts for less than 1 per cent of all mammary tumors [9] but is the form of sarcoma most frequently observed.

The symptoms are fairly characteristic. There is usually a history of a preceding lump which, having remained stationary or having slowly increased in size for a variable period of years, suddenly becomes transformed into a rapidly enlarging mass—a change sometimes initiated by trauma. Occasionally, growth is rapid from the beginning. Although the growth is usually single, multiple nodules are sometimes observed, and rarely the disease may be bilateral. The chief signs of carcinoma, i. e., nipple retraction, cutaneous edema and fixation, are generally lacking. Ulceration of the skin and pain are late symptoms and develop only after the tumor has attained an immense size. These skin changes, if present, are a result of pressure atrophy and do not represent true invasion.

On examination, the tumor appears as a well circumscribed, freely movable and sometimes cystic mass. The surface is usually smooth, although in the larger growths it may be indefinitely nodular (fig. 1). The axillary nodes are small, soft and freely movable, except when enlarged owing to inflammatory hyperplasia.

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9. Funck-Brentano, P.; Bertrand, I., and Poilleux, F.: Les tumeurs phyllodes du sein. (Cystosarcoma phyllodes de Johann Müller), J. de chir. **51**:506, 1938. Greenough, R. B., and Simmons, C. C.: Fibro-Epithelial Tumors of the Mammary Gland, Ann. Surg. **54**:517, 1911. Warren, J. C.: The Surgeon and the Pathologist, J. A. M. A. **45**:149 (July 15) 1905.

Grossly, the tumor is spherical and encapsulated; ramifications of the capsule often extend into the substance and form indefinite lobules or nodules. The surface is frequently uneven and irregular. The consistency is variable but usually moderately firm, unless extensive necrosis and cyst formation have supervened. The cut surface is bulging, grayish white or pinkish gray, whorled and elastic. In the intracanalicular variety, the growth is traversed by clefts into which polypoid masses

Fig. 1 (case 6).—Adenofibrosarcoma. A typical example is shown. Note the large size, the spherical shape and the nodular surface of the tumor. The skin is thin and stretched and the nipple flattened, but these structures are not invaded.

may project so that these clefts have a branched or stellate appearance (fig. 2). Cysts, if present, are of two types: (1) those resulting from continued secretion of the epithelial cells and lined by a smooth glistening membrane; (2) those produced by necrosis and liquefaction. The pericanalicular type is usually smaller, firmer and seldom cystic. Sometimes, the remnants of a preexisting fibroadenoma can be distinguished.

Microscopically, the picture is variable, although there are two extremes between which all gradations occur. At the one extreme the similarity to fibroadenoma is well retained; the only difference is in the increased cellularity of the stroma and the presence of scattered mitoses and bizarre cell forms. Myxomatous changes often occur, and Lee and Pack [5] stated that "the metaplasia of the stroma into such tissue is the distinguishing and essential feature of the intracanalicular variety." The epithelial components may be scarce or fairly prominent, but hyperplasia is infrequent. Squamous metaplasia sometimes occurs, and occasionally epithelial pearls are formed. At the other extreme is a

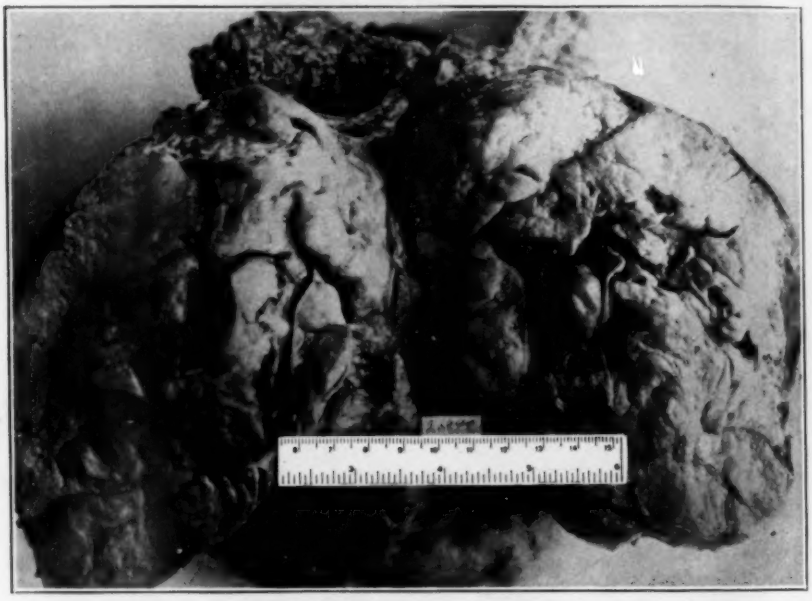

Fig. 2 (case 6).—Adenofibrosarcoma. The tumor is encapsulated and cystic. Smooth-lined polypoid masses often project into the cysts and the clefts.

highly cellular appearance, the tumor being composed of indefinitely spindle or polymorphous cells separated by little collagen. Mitoses, giant cells and atypical cells are numerous, and the stroma has a true sarcomatous appearance. The epithelial elements form only a minor part of the structure, are widely scattered and in some parts of the tumor may be lacking. As a rule, the majority of the neoplasms fall somewhere between these two extremes.

The sarcomatous change may be diffuse and fairly uniform throughout the fibroadenoma, so that the entire mass appears to have been trans-

formed at the same time. Tumors of a certain group, however, have a patchy appearance in that parts of the tumor are highly cellular, while other portions are relatively acellular and hyalinized. The impression is gained thereby that fibroadenoma is being replaced by sarcoma originating from a single focus within it (fig. 3). Although most of the tumors are bounded by a compression capsule, direct contact with the adjacent fat may be present. The surrounding portion of the breast shows no changes which are constant or characteristic.

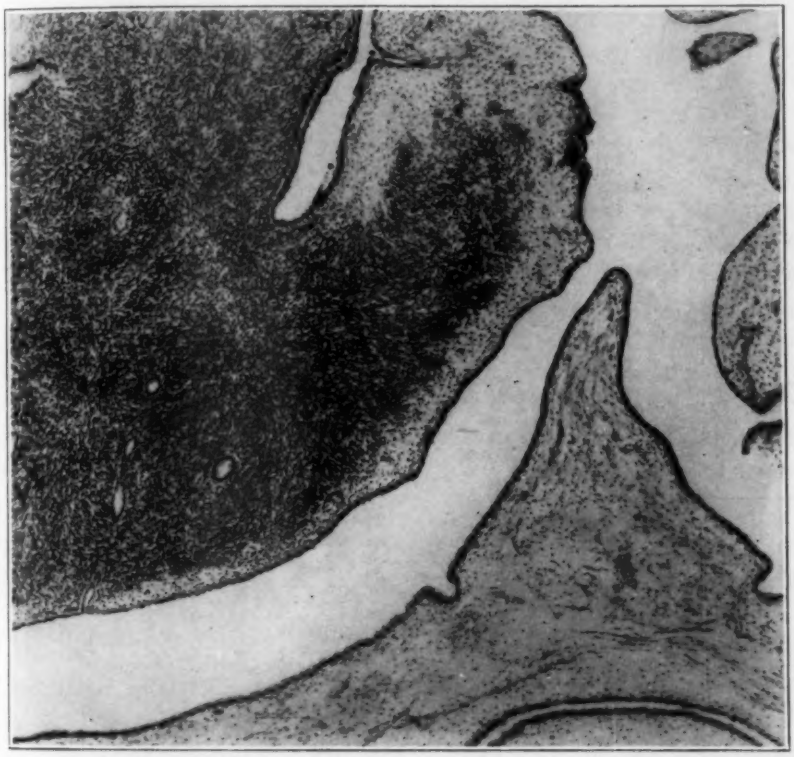

Fig. 3 (case 2).—Adenofibrosarcoma. A characteristic intracanalicular fibroadenoma with uneven distribution of the sarcomatous transformation is shown. Note the uninvolved zone just beneath the epithelium.

As to prognosis, most observers agree on the generally innocent course of the disease. Distant metastasis has been reported by Billroth,[10]

10. Billroth, T.: Diseases of the Female Mammary Glands, in Grandin, E. H.: Cyclopaedia of Obstetrics and Gynecology, New York, William Wood & Company, 1887, vol. 9, pp. 51, 56 and 71.

Prym,[11] Sophian,[12] Fox, Guérin [13] and Johnsrud,[14] but it is a rare complication. Metastasis to the axilla probably never occurs. Local recurrence followed by metastasis has been noted [15]; the tumors usually recur as fibrosarcoma and metastasize in this form. Local recurrence alone is supposedly more common, and some of the first writers on the subject had strikingly high percentages for this feature. However, Lee and Pack found only 6 recurrences in 91 reported cases in which the outcome was known, and Harrington and Miller [16] observed this complication in only 1 of 24 cases of fibroadenoma. It seems unlikely that recurrence plays a prominent role except in a small number of cases. Further, there is always the possibility that apparent recurrence may represent an entirely new tumor.

Local excision is adequate therapy unless the tumor is exceptionally large; this is a factor which sometimes necessitates a more extensive procedure for complete removal of the growth. Should recurrence appear, it is probably better then to perform simple mastectomy. There is no way to determine which tumors of this group will show malignant tendencies; only the subsequent course of the patient can answer the question. The chief danger is that the tumor in question may recur as fibrosarcoma with the correspondingly increased threat of distant spread.

In this laboratory 15 tumors have been accepted as belonging to this class. Certain large cellular growths classed as fibroadenoma but showing none of the cellular changes commonly associated with malignant tumor have been excluded. The 15 tumors mentioned constitute 2.1 per

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11. Prym, P.: Fibrocystadenoma sarkomatosum der Mamma mit Metastasen, Frankfurt. Ztschr. f. Path. **10**:60, 1912.

12. Sophian, L. H.: Adenofibrosarcoma of the Breast, Arch. Path. **9**:1007 (May) 1930.

13. Guérin, P.: Sarcome à cellules géantes du sein par transformation d'un fibro-adénome latent, Bull. Assoc. franç. p. l'étude du cancer **25**:326, 1936.

14. Johnsrud, R. I.: Sarcoma of Breast, Northwest Med. **39**:27, 1940.

15. (*a*) Finsterer, J.: Ueber das Sarkom der weiblichen Brustdrüse, Deutsche Ztschr. f. Chir. **86**:352, 1906-1907. (*b*) Hartmann, H.; Bertrand-Fontaine, T., and Guérin, P.: Sur trois cas de sarcomes à cellules géantes du sein, Bull. Assoc. franç. p. l'étude du cancer **22**:378, 1933. (*c*) Hoffmann, A.: Ein durch die grosse Zahl der Recidive, sowie durch einen ausnahmsweise langdauernden recidivfreien Intervall bemerkenswerther Fall von Mammasarcom, Arch. f. klin. Chir. **48**:93, 1894. (*d*) White, J. W.: Malignant Variant of Cystosarcoma Phyllodes, Am. J. Cancer **40**:458, 1940. Sophian.[12]

16. Harrington, S. W., and Miller, J. M.: Lymphosarcoma of the Mammary Gland, Am. J. Surg. **48**:346, 1940; Fibrosarcoma of the Mammary Gland, Surgery **7**:129, 1940; Malignant Changes in Fibroadenoma of the Mammary Gland, Surg., Gynec. & Obst. **70**:615, 1940; A Mixed Tumor (Carcinosarcoma) of the Breast, Surgery **7**:122, 1940.

cent of all tumors removed with the diagnosis of fibroadenoma. The average age of the patients was 47.3 years, with extremes of 33 and 69 years. Ten tumors belonged to the intracanalicular variety; 2 were of mixed types, 2 were undetermined, and 1 was of the pericanalicular type. The average duration of symptoms was seventeen and eight-tenths

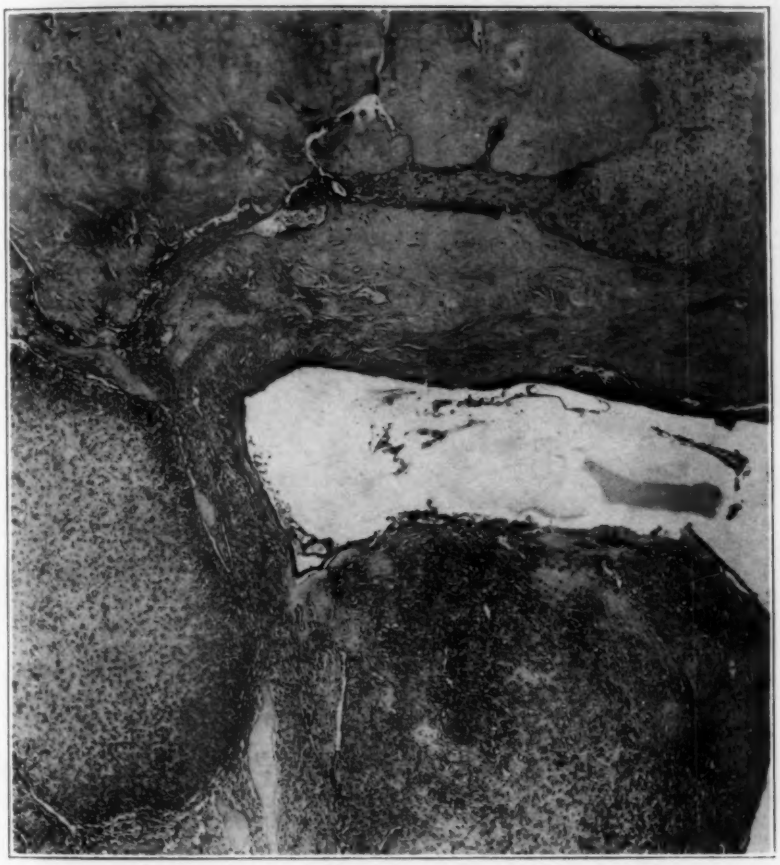

Fig. 4 (case 15).—Intracanalicular fibroadenoma with focal sarcomatous changes. There are areas of cartilaginous metaplasia both within the actively growing and within the acellular parts.

months, with one exception, a tumor which had been present for forty-two years. The period of rapid growth, however, averaged only six months, varying between one and twelve months. The smallest tumor was 3.5 cm. in diameter; the largest weighed 14 pounds (6.4 Kg.).

Seven of the patients were subjected to radical mastectomy, 5 had simple mastectomy, and 3 had only local excision. In no case in which the axilla was removed was there involvement of the lymph nodes. Nine patients have been followed, 5 have been lost sight of, and 1 died after operation. Six patients have lived from six to nineteen years without evidence of recurrence or metastasis, 1 died four years after operation from intercurrent causes, and 2 others are living after eighteen and twenty-five months without return of their disease. There was squamous metaplasia of the epithelium in 3 cases, and cartilaginous metaplasia of the stroma in 2 (figs. 4 and 5).

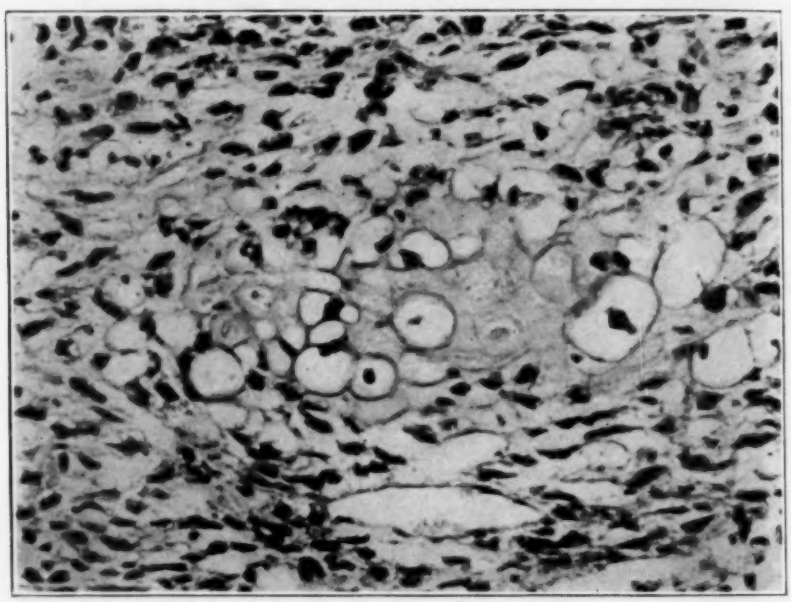

Fig. 5 (case 14).—Adenofibrosarcoma. Note a metaplastic focus of cartilage among the tumor cells.

FIBROSARCOMA

Fibrosarcoma is the most frequently encountered variety of pure sarcoma, but, even so, the number of cases is small. It originates from the ordinary connective tissue of the breast, i. e., the interlobar and interlobular fibrous tissues, and its behavior is similar to that of fibrosarcoma elsewhere.

The spindle cell, polymorphous cell, round cell, mixed cell, neurogenic and osteoid types of sarcoma, as well as myxosarcoma, are considered here, since most of them are primarily derived from connective tissue

and simply represent poor differentiation with the result that the fibroblastic nature of the growth is less evident. The majority of the round cell growths are probably lymphosarcoma and atypical carcinoma, although a few may be highly undifferentiated fibrosarcoma (fig. 6). There is no necessity to retain the term "myxosarcoma" since this ordinarily denotes a degenerative change in what is otherwise fibrosarcoma or adenosarcoma. Neurogenic sarcoma has been reported by Fox, Sailer and Stewart and Copeland,[17] but it is closely allied to fibrosarcoma, and there seems little need to keep this subdivision. Further,

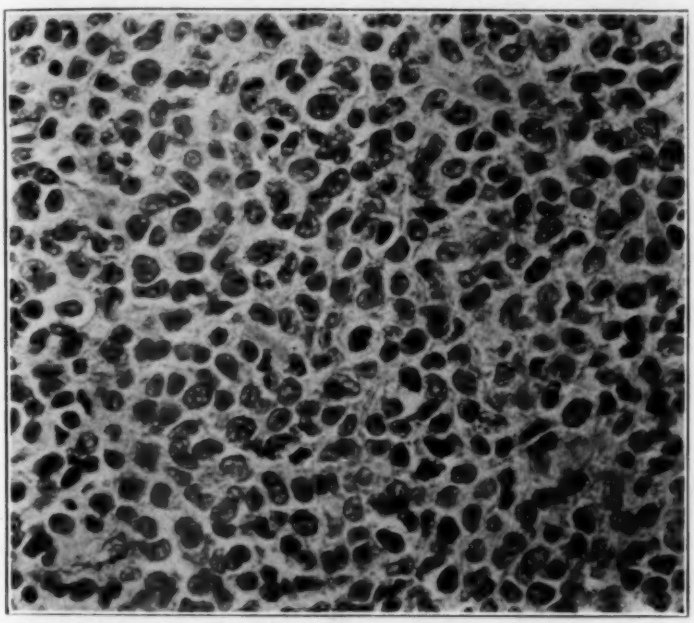

Fig. 6 (case 20).—Fibrosarcoma. The primary tumor composed of rounded cells is shown; its true nature was recognized only in the recurrence (see fig. 7).

if one accepts the theory of metaplasia, most tumors classified as osteoid chondrosarcoma or osteochondrosarcoma can be considered primarily fibrosarcoma with secondary development of osseous or cartilaginous tissue and thus are better classified as fibrosarcoma with osteoid metaplasia or as teratoid tumors. It is seldom necessary to explain their development on the basis of teratoma.

17. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, Am. J. Cancer **15**:1235, 1931.

Fibrosarcoma may occur at any age. Sheild [18] noted myxosarcoma in the breast of an infant 6 months old. At the other extreme is the observation of Graves [19] of a 12 pound (5.4 Kg.) spindle cell sarcoma in a 98 year old woman who ultimately died from pulmonary metastases. In most cases fibrosarcoma develops between the ages of 35 and 65 years, with an average age of 45 to 50 years, and therefore somewhat earlier in life than carcinoma.[20]

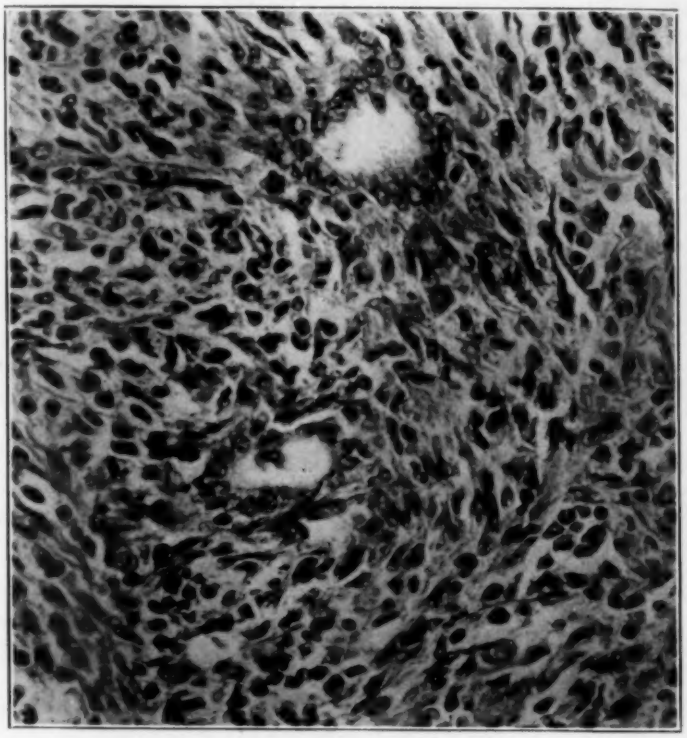

Fig. 7 (case 20).—Fibrosarcoma: A recurrent nodule with the tumor cells now spindle shaped and with intercellular collagen fibers indicating its fibroblastic character. Two incorporated ducts are present.

Although the vast majority of the tumors diagnosed as fibrosarcoma occur in females, a few are found in males and form a proportionately

18. Sheild, A. M.: Diseases of the Breast, London, Macmillan & Company, 1898, p. 264.

19. Graves, T. C.: Mammary Sarcoma of Old Age, Brit. M. J. **1**:81, 1920.

20. Deaver, J. B., and McFarland, J.: The Breast: Its Anomalies, Its Diseases, and Their Treatment, Philadelphia, P. Blakiston's Son & Co., 1917, pp. 372-442.

higher percentage of the total number of benign or malignant neoplasms. Neal [21] found 10 tumors classified as sarcoma among 308 mammary lesions in males and 5 of these were fibrosarcoma. They appeared in a younger age group than did the tumors classified as carcinoma.

The symptoms are much the same as for adenosarcoma, and it is often impossible to differentiate between the two neoplasms. Ordinarily fibrosarcoma shows a greater tendency toward slow progressive enlarge-

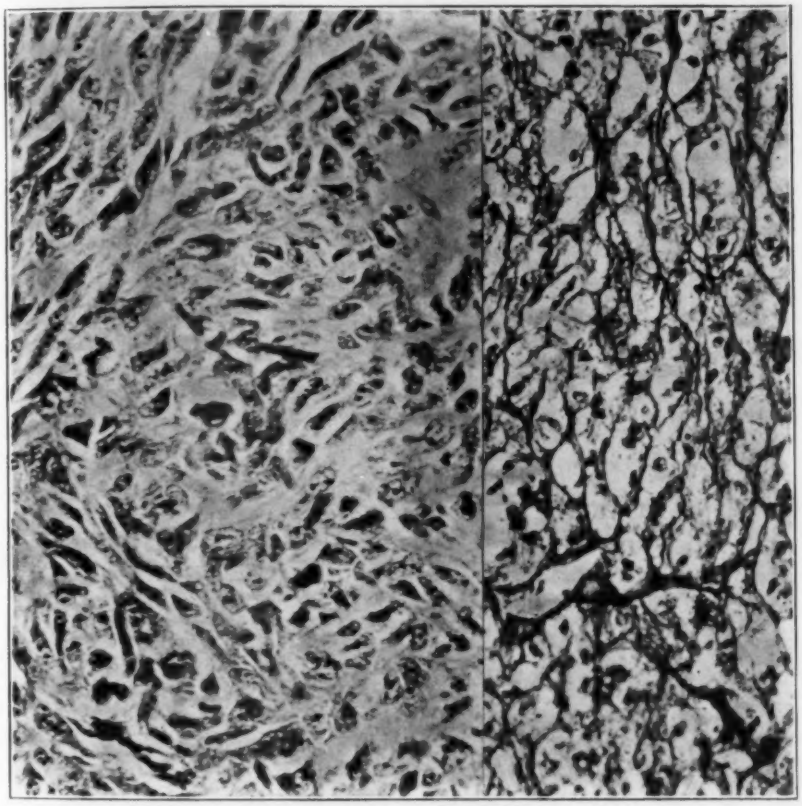

Fig. 8 (case 17).—Fibrosarcoma. The anaplastic cellular structure is shown on the left; on the right a Laidlaw silver reticulin stain shows connective tissue fibers wrapped around the tumor cells.

ment from the beginning, and the sometimes huge size of adenosarcoma is seldom seen, although large tumors have been observed.[22] It is a firm

21. Neal, M. P.: Malignant Tumors of the Male Breast, South. M. J. **25**:841, 1932.

22. Cathcart, R. S.: Massive Sarcoma of Breasts, South. Med. & Surg. **92**: 810, 1930.

well circumscribed solid tumor which is usually freely movable and seldom adherent to the skin or the pectoral fascia.

Grossly, it is a well outlined, moderately firm spherical tumor having a more or less homogeneous grayish white to pinkish gray bulging cut surface. Clefts and cysts as found in adenosarcoma are not seen. The tissue not infrequently has an irregular whorled appearance, and foci of necrosis and hemorrhage may be present.

Microscopically, the picture is dependent on the degree of differentiation. In the better differentiated fibrosarcoma, the resemblance to

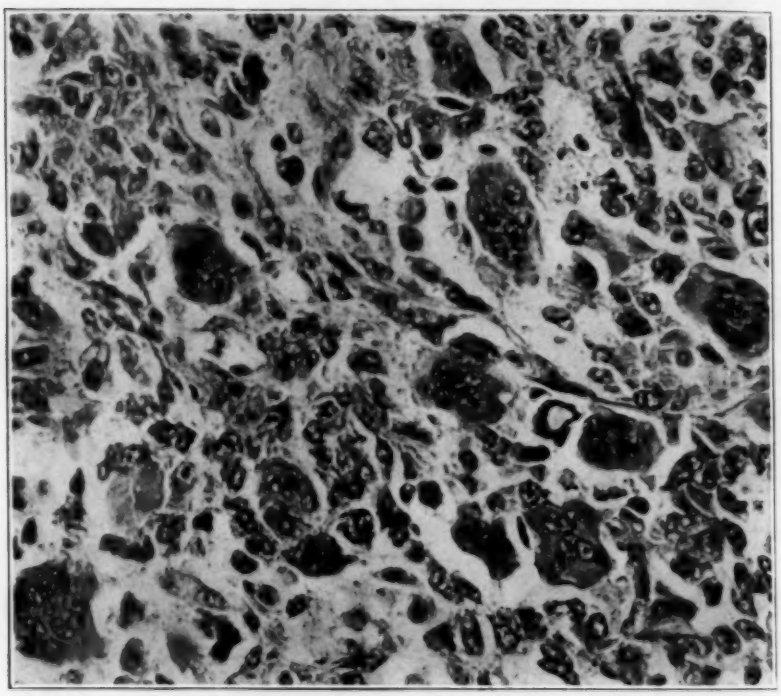

Fig. 9 (case 20).—Fibrosarcoma. Another area from a recurrent nodule showing the presence of numerous giant cells.

fibroma is marked, while in the undifferentiated and anaplastic forms, cellular pleomorphism, mitotic figures and giant cells are prominent features (fig. 8). Giant cells, if present, are of two varieties: (1) the true tumor giant cell, formed as a result of rapid growth and incomplete cell division after nuclear division, and (2) the foreign body giant cell, produced as a reaction to cellular necrosis, osteoid formation and similar changes. Sometimes giant cells may be exceptionally numerous, but there is no necessity to designate the neoplasms in which they are seen

as giant cell sarcoma (fig. 9). Epithelial elements are generally lacking but, if found, are represented by atrophic ducts incorporated in the periphery of the growth (fig. 10). Occasionally there are extensive bands of necrosis so that viable tumor cells are localized to the vicinity of blood vessels, and this feature has led to the mistaken diagnosis of perithelioma or angiosarcoma. Foci of osseous, osteoid or cartilaginous tissue are sometimes seen (fig. 11). Although usually encapsulated, the neoplasm may extend directly into the adjacent fat.

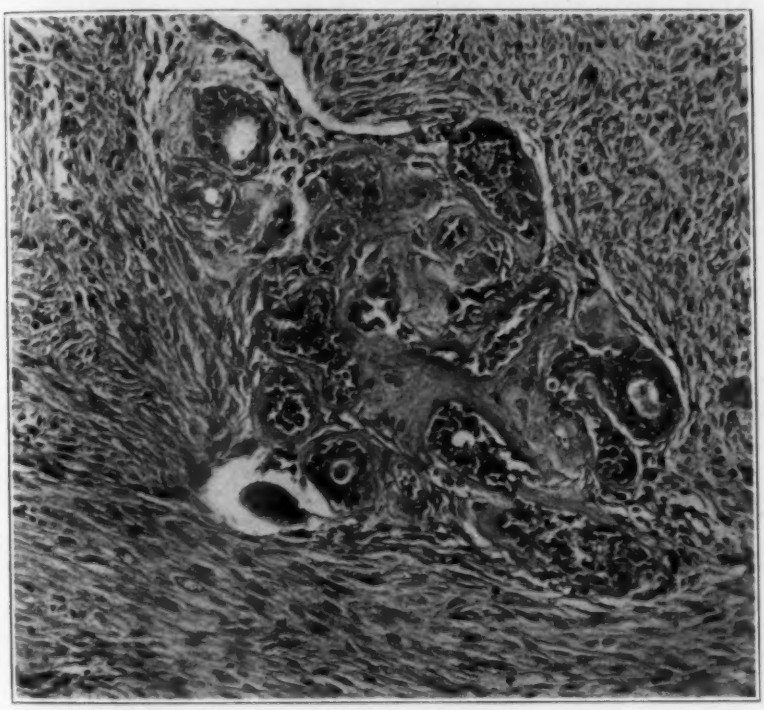

Fig. 10 (case 18).—A differentiated fibrosarcoma with incorporation of mammary ducts at its periphery. Although these ducts are compressed and atrophic, they maintain their usual lobular arrangement.

The tendency toward recurrence and metastasis is much greater than that in adenosarcoma, but the degree of malignancy is less than that of carcinoma. Metastasis, when it occurs, does so by way of the blood stream, and the lungs are the most frequent site. In 3 of 5 cases reported by Schreiner and Thibaudeau metastasis developed, and in a single case involving the male breast death occurred. In 4 of 9 cases reported by Harrington and Miller there was no evidence of the disease after four to seventeen years. In 2 of these 4, locally recurrent tumors had been

removed, and in 1 of the other 2 cases death ultimately resulted from the disease. Boldrey noted recurrences in 2 of 4 cases. Among 15 patients with fibrosarcoma whose cases were recorded by Finsterer, there were 4 who were free from recurrence, 3 who had local recurrences, 3 who suffered internal metastasis and 5 who were unknown or dead from intercurrent causes. Fox stated that a fatal termination occurred in 26.7 per cent of his cases but that only 33.3 per cent of the patients were

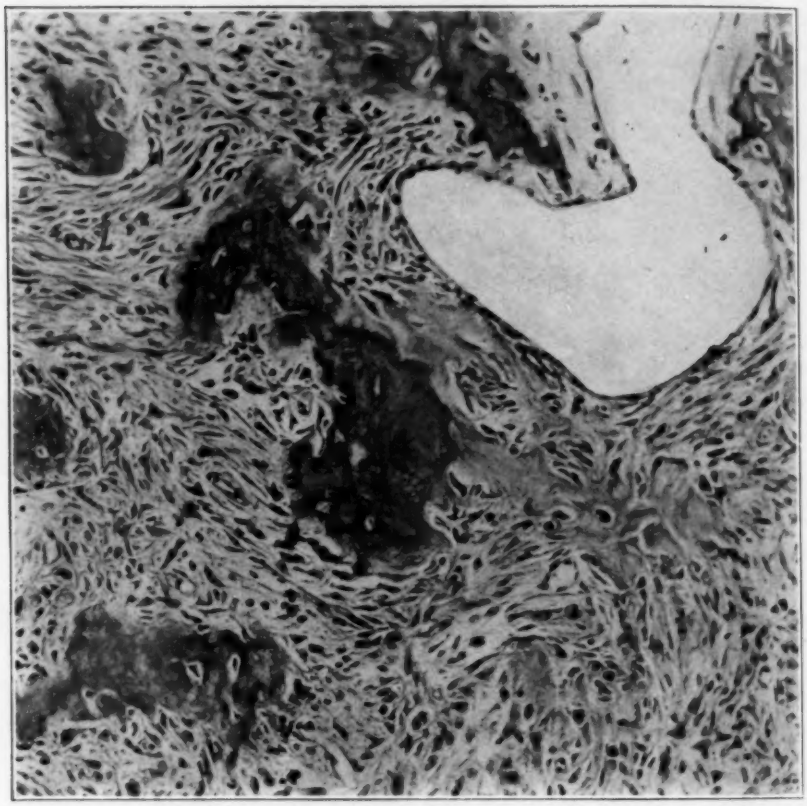

Fig. 11 (case 18).—Fibrosarcoma, showing the formation of osteoid tissue near the center. The adjacent tumor tissue merges almost imperceptibly with the osteoid elements.

known to be alive more than one year, while the mortality rate in cases of neurogenic sarcoma was 42.9 per cent. Rose, however, found that 5 patients out of 6 were living after one to twenty-three years, while the sixth had died six months after operation. An interesting case of local recurrence is that reported by Smith and Bartlett in which twenty-seven operations in all were undertaken for the primary and the recurrent growths; death finally resulted five years after the first operation.

Mastectomy with removal of the pectoral muscles is recommended by most writers as the method of choice, since the tumor may extend beyond the confines of its capsule. Wide local excision, though, has sometimes been employed with success. Repeated recurrence need not necessarily imply a hopeless outlook, since there is the case of Gross [23] in which the patient was subjected to twenty-three operations with removal of fifty-one separate tumors and final complete eradication of the disease. When the condition does progress to a fatal termination, it ordinarily has a more protracted course than carcinoma.

Our observations include 5 tumors diagnosed as fibrosarcoma. Three were well differentiated, and 2 were poorly differentiated. Four of the patients have been followed, and 2 are living and well without recurrent or metastatic disease after six and eleven years, respectively. Another patient is living five years after operation but with generalized metastases, which first appeared three years after radical mastectomy. Another patient had local removal of a tumor which on gross examination was believed to be cellular fibroadenoma. Microscopically, its true nature was appreciated. Recurrences developed six months later, and radical mastectomy was done. The patient finally died from generalized metastases, the entire course of the disease having covered about two years.

The average age of these patients was 36 years, which was some ten years less than that of patients with adenosarcoma, with variations between 26 and 48 years. The average duration of symptoms was four and nine-tenths months.

LYMPHOBLASTOMA

Lymphoblastoma as the designation of a group includes lymphosarcoma, leukemic tumors, chloroma and Hodgkin's disease. All are rare in the breast, but lymphosarcoma is perhaps the most frequent. There are three general types: (1) that in which the process is localized to the breast; (2) that in which the first evidence of the disease appears in the breast and is later found to be part of a generalized process, and (3) that in which the breast involvement is but one manifestation of a systemic disease.

Lymphosarcoma.—Lymphosarcoma begins as a small tumor which enlarges rapidly and often produces symptoms and signs suggestive of carcinoma, so that radical mastectomy has been done because that type of neoplasm has been diagnosed. When lymphosarcoma is localized to the breast, the diagnosis can usually be made only after microscopic study. There may be single or multiple nodules, and the disease is sometimes bilateral. The axillary nodes are usually involved. Cases in which

23. Gross, S. D.: System of Surgery, Philadelphia, Henry C. Lea's Son & Co., 1882, p. 974.

it was associated with pregnancy have been reported by Elsberg [24] and by Schleiter and Bruecken.[25] There is no particular age distribution.

Grossly, there is usually a fairly well circumscribed, moderately firm nodule having a grayish white or pinkish gray homogeneous glistening cut surface. Occasionally, the disease is less well localized, and the general structure of the breast is preserved near the periphery of the lesion, where the lobules are enlarged and accentuated. Microscopically,

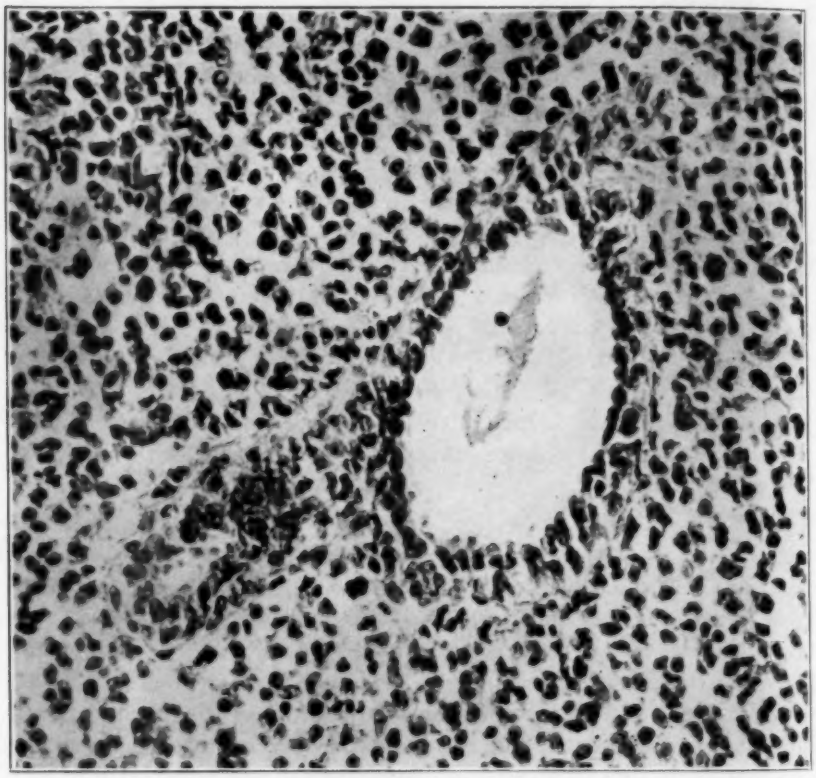

Fig. 12 (case 22).—Lymphosarcoma. The cells are evenly and uniformly distributed and approach the size of reticulum cells. An incorporated duct is present. The irregularity in cell shape is the result of shrinkage during fixation.

either the reticulum cell or the lymphocytic type may be found. The cells infiltrate the tissue diffusely and are closely packed near the center of the mass, where there may be only atrophic remnants or a complete absence of mammary structures (fig. 12). In the outer zones they are

24. Elsberg, C. A.: Multiple Lymphosarcoma of Both Breasts, Ann. Surg. **60**: 767, 1914.

25. Schleiter, H. G., and Bruecken, A. J.: Lymphosarcoma Involving Both Breasts, Atlantic M. J. **29**:693, 1926.

more scattered and are often confined chiefly to incompletely replaced lobules.

The origin of these cells is still uncertain. Since lymphocytes are not found in the normal breast, one explanation offered is that they appear in association with chronic cystic mastitis or some inflammatory process and later undergo malignant proliferation. Another theory is that the tumor arises in outlying glands and extends into the substance of the breast so that at the time of examination the mammary gland seems to be the primary site.

The treatment is irradiation or surgical removal or a combination of both. When the disease is recognized, radiotherapy is perhaps the method of choice, although there are examples of good results following surgical excision of localized lymphosarcoma of other regions. In any event, when operation is the primary method chosen, the axilla also should be removed, and it may be advantageous to follow such a procedure with a course of radiotherapy. Generally speaking, the course is rapidly fatal, although a few examples of long survival are recorded; Schreiner and Thibaudeau reported a survival of four years and nine months; Harrington and Miller, one of six years.

Hodgkin's Disease.—Hodgkin's disease appears rarely, if at all, in the breast as a local disease. Kückens [26] mentioned the case of a girl of 17 with a lesion apparently restricted to the breast. Mastectomy was done on the basis of a diagnosis of cancer, and microscopic examination showed numerous eosinophils, leukocytes, plasma cells and typical Sternberg cells. He assumed that the disease had originated in the lower axillary nodes, with subsequent extension into the breast. The case of Middleton [27] also belonged to this category. Schultz [28] referred to 2 cases of Kaufmann in which the breast was involved in a generalized process. In 1 of these, however, eosinophils, Sternberg cells, necrosis and fibrosis were lacking in the breast lesion. He adds another example with involvement of cervical, axillary and mediastinal lymph nodes. The signs and symptoms are much the same as for lymphosarcoma, and diagnosis is possible only after histologic examination. Radiotherapy offers the only rational treatment.

Leukemic Tumors.—Leukemic tumors form a perplexing group of mammary neoplasms. Not infrequently such tumors have been removed

26. Kückens, H.: Ein lokales Lymphogranulom der Brust in Form eines Mammatumors, Beitr. z. path. Anat. u. z. allg. Path. **80**:135, 1928.

27. Middleton, W. S.: Some Clinical Caprices of Hodgkin's Disease, Ann. Int. Med. **11**:448, 1937.

28. Schultz, A.: Die Lymphogranulomatose der Brustdrüse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1933, vol. 7, pt. 2, pp. 169-173.

because of a diagnosis of carcinoma or lymphosarcoma with the later discovery that the patient was suffering from leukemia. In the older reports, a satisfactory examination of the blood had not always been made prior to operation, so that it is impossible to say whether or not the breast represented the first manifestation of the disease other than from a clinical standpoint. Haram [29] reported a case, however, in which the blood film was normal when the breast tumor first appeared. Later, when the opposite breast was the seat of similar nodules, the blood

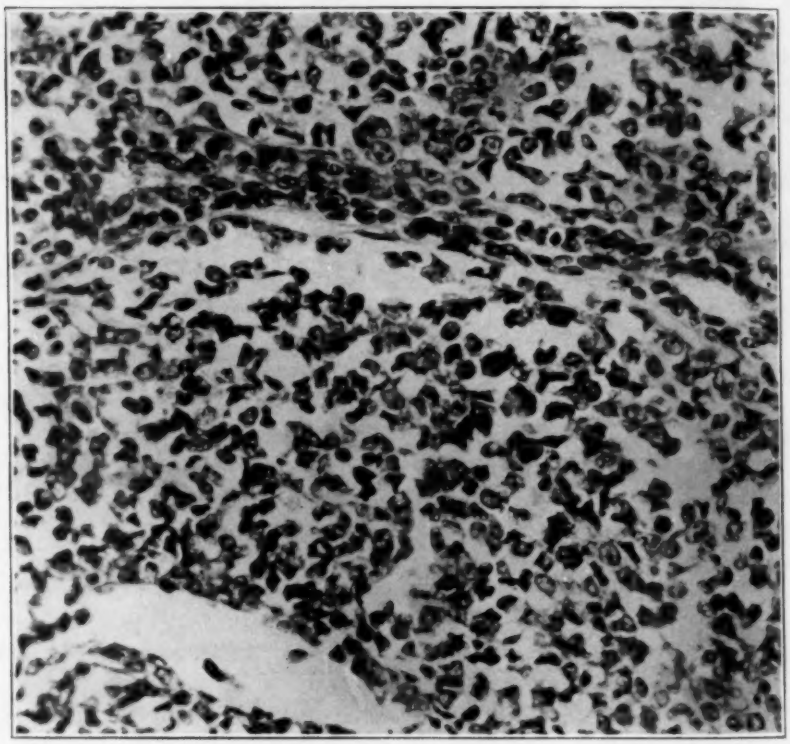

Fig. 13 (case 23).—Myeloid leukemia. The cells closely resemble those of lymphosarcoma. A compressed duct is present. The blood changes appeared after removal of the breast tumor.

showed a leukemic picture. The majority of the examples, though, have been associated with leukemic change in the blood. This may be either myeloid (fig. 13) or lymphoid (fig. 14) leukemia and is usually the acute type. Grossly and microscopically, the appearance of the nodules

29. Haram, B. J.: Lymphatic Leukemia with Bilateral Mammary Changes, Lancet **1**:1277, 1937.

is similar to that of lymphosarcoma, and there are no differential characteristics. The course of the disease is one of rapid development and short duration.

Chloroma.—Chloroma embraces a group closely allied to the leukemic tumors. It appears most frequently in the short flat bones but is sometimes found in the breast, either as an isolated process or as a part of a more widespread condition. In almost all of the cases it is associated with leukemia; a notable exception is the case reported by Reid [30] in which up to the time of death the blood findings were relatively normal.

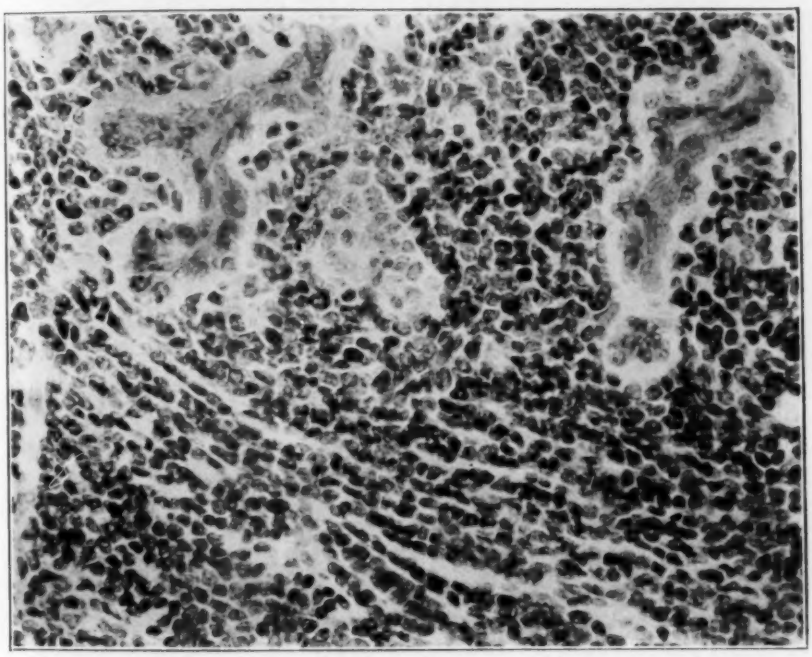

Fig. 14 (case 14).—Lymphatic leukemia. The tumor cells infiltrate the tissue evenly and diffusely, compressing and separating the included ducts.

The earlier writers on this subject expressed the belief that the blood changes were those of lymphatic leukemia, but more recent observers have found that the myeloid form is the more common. Kandel [31] concluded that almost all of the cases belong to the myeloid group and that the older reports were probably in error because of the poorer histologic technics current at that time. The characteristic feature of the disease

30. Reid, M.: Ueber ein doppelseitiges myeloides Chlorom der Mamma, Beitr. z. klin. Chir. **95**:47, 1915.

31. Kandel, E. V.: Chloroma: Review of the Literature from 1926 to 1936 and Report of Three Cases, Arch. Int. Med. **59**:691 (April) 1937.

is, of course, the green color. Most of the cases terminate fatally within a few months, and even if the blood differential count is normal at the time of the first appearance of the tumor, subsequent examinations will reveal the true nature of the disease.

Two neoplasms observed in this laboratory have been diagnosed as lymphosarcoma and 2 as leukemia. There have been no examples of Hodgkin's disease or of chloroma. Diagnosis of 1 tumor classified as lymphosarcoma is uncertain, since the mass was removed incidentally from the breast of a patient who died after decompression for a brain tumor. No cerebral tissue was removed, and permission for an autopsy was not obtained. Therefore, the relation between the two lesions, if any, was never learned, and the classification has been made largely on histologic grounds. The other tumor appeared in a 54 year old woman who had radical mastectomy after a biopsy diagnosis of probable lymphosarcoma. Postoperative roentgen therapy was given, but the disease is of too recent occurrence to draw any conclusions as to the outcome. One of the leukemic neoplasms occurred in a 33 year old woman on whom local excision of a breast nodule believed to be benign lymphoma was done. Recurrence and involvement of the opposite breast led to bilateral radical mastectomy. Unfortunately, a blood count was not taken until after this operation; at this time typical lymphatic leukemia was found. The disease progressed to a fatal termination about six months after the first symptoms were noted. In the other patient, the first manifestation of the disease was a breast nodule; this was removed and thought to be lymphosarcoma. A short time later she returned to the hospital because of generalized symptoms, and a blood count then showed acute myeloid leukemia. Death ensued shortly thereafter; the entire course of the disease lasted only two months.

MALIGNANT HEMANGIOENDOTHELIOMA

Angioma, benign or malignant, occurring in the substance of the breast is unusual, and the number of authentic examples of the malignant form recorded in the literature is small. In the majority of instances a tumor of this type found in this region is cutaneous in derivation, and although the breast may have been involved by direct extension of the growth, the tumor should not be incorporated with those of true intramammary origin.

Since malignant angioma is infrequent, it is difficult to determine the actual proportion of malignant with respect to benign forms. There is a somewhat general belief that hemangioma of the breast is more prone to malignant change than hemangioma of other parts. To support this view

there is the observation of Menville and Bloodgood [32] that in 11 per cent of the cases in their series the tumor was malignant. That no deductions can be drawn from such a result, however, is obvious as there were only 9 tumors diagnosed as angioma in a total of 3,000 breasts. For all cases of angioma, Geschickter and Keasbey [33] estimated that malignant characteristics were shown in less than 1 per cent.

Two types of benign angioma are found, the capillary and the cavernous. The former is the more common, and is difficult to differentiate from one of the malignant varieties which, seemingly benign from a histologic standpoint, ultimately metastasizes. Furthermore, hemangioma present for years as a benign growth may become malignant under the influence of trauma or recurrence.

Tumors diagnosed as malignant hemangioendothelioma can be divided into three general classes. In the first, the microscopic picture of both the primary and the metastatic lesion resembles that of simple angioma, and satisfactory criteria for early recognition are usually lacking. This benign appearance has led to the term "benign metastasizing hemangioma." The cases of Borrmann [34] and Ewing [35] belong to this class. The second type is more intermediate in character. The primary or initial tumor appears well differentiated and innocent, but the recurrent or the metastatic growth assumes a malignant aspect. Typical examples are those of Sherry,[36] Pulford [37] and Robinson and Castleman.[38] The third division includes those tumors recognizable as malignant from the beginning; they are illustrated in the cases of de Bary,[39] Da Costa [40] and Menville and Bloodgood.

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32. Menville, J. G., and Bloodgood, J. C.: Subcutaneous Angiomas of the Breast, Ann. Surg. **97**:401, 1933.

33. Geschickter, C. F., and Keasbey, L. E.: Tumors of Blood Vessels, Am. J. Cancer **23**:568, 1935.

34. Borrmann, R.: Metastasenbildung bei histologisch gutartigen Geschwülsten (Fall von metastasierendem Angiom), Beitr. z. path. Anat. u. z. allg. Path. **40**:372, 1906.

35. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 249-261 and 548-560.

36. Sherry, L. B.: Report of a Case of Hemangioma of the Breast, West. J. Surg. **42**:318, 1934.

37. Pulford, D. S., Jr.; Neoplasms of the Blood-Lymph-Vascular System with Special Reference to Endotheliomas, Ann. Surg. **82**:710, 1925.

38. Robinson, N. M., and Castleman, B.: Benign Metastasizing Hemangioma, Ann. Surg. **104**:453, 1936.

39. de Bary, E.: Ueber zwei Fälle von malignem Hämangioendotheliom, Frankfurt. Ztschr. f. Path. **46**:410, 1933.

40. Da Costa, J. C.: A Case of Endothelioma of the Mammary Gland, Am. Med. **5**:1024, 1903.

Incorporation of the first group in the malignant one has been criticized because of the possibility of a multicentric origin, a viewpoint hard to disprove. The presence, however, of an intermediate group of tumors which, originally considered innocuous, have produced recurrent or metastatic growths of undoubted malignant character seems strong evidence in favor of a single originating focus, with the reservation that surgical intervention may have been the stimulus inducing the malignant transformation. Another consideration, suggested by Borrmann, is that hemangioendothelioma is truly malignant from the beginning and that the histologic criteria are at fault. An illustrative example of this factor is found in a case in our series in which a tumor at first called capillary hemangioma showed on retrospect a few changes which might have suggested its true character. A somewhat analogous situation is found in certain cases of carcinoma of the thyroid in which the primary growth and lesions accepted as secondary deposits have revealed no microscopic cytologic changes suggesting malignancy.

Clinically, the diagnosis is difficult. Ordinarily the appearance is that of a rapidly enlarging unilateral tumor, which may be circumscribed or diffuse and irregular. Early the tumor tends to be soft and compressible, quickly assuming its former size when the pressure is released. After thrombosis and fibrosis have taken place, the consistency becomes more firm. Symptoms of pain, fluctuation and bruit are inconstant. The skin may or may not be involved and therefore is not always discolored, although when uninvolved, the dusky color of the tumor can sometimes be seen through it. The growth appears dark on transillumination and may attain a considerable size. A history of preexisting tumor of long duration is occasionally elicited.

The gross pathologic appearance is that of a soft spongy hemorrhagic mass, either circumscribed or infiltrating and often collapsing to some extent when sectioned. Microscopically, the picture varies from the well differentiated forms having the aspect of ordinary hemangioma to the highly cellular types showing little tendency to form recognizable vascular spaces. Foci of necrosis, hemorrhage and fibrosis are not infrequent. Remnants of breast structures may be found near the periphery.

The course is variable in its rapidity and largely dependent on the specific type concerned. The better differentiated tumors tend to grow slowly and metastasize late, while the more highly cellular forms often pursue a rapid course. Metastasis, when it occurs, is systemic; the axillary lymph nodes are rarely, if ever, involved. The prognosis is ostensibly poor since death resulted in 5 of 8 reported cases accepted

as clearly belonging to this group, and in 2 of the remainder the outcome was unknown or dubious. Both patients observed in this institution died.

Various methods of therapy have been advocated, but adequate surgical removal seems the best. Radiotherapy has been recommended and used but certainly without much success. In our experience, it has had no appreciable effect.

REPORT OF CASES

CASE 25.—A single white Jewish woman, aged 19, was admitted on July 30, 1935, to the outpatient department of the Presbyterian Hospital and Sloane Hospital for Women to the service of Dr. David C. Bull, with a slight blue discoloration of the skin just above the nipple of the right breast of three months' duration. A lump had appeared in this region during the last week before admission. Although at first painless, it had later become slightly tender. There was no history of trauma.

Physical examination revealed that the right breast was slightly larger than the left and that there was some retraction of the nipple. The areola was enlarged, and the upper half of it was faint blue. A firm smooth freely movable mass measuring about 3 by 2 by 1.5 cm. was felt beneath this area, and another similar mass was found immediately inferior to the nipple. The blue color was believed due to venous congestion, and the breast changes were considered those of chronic cystic mastitis. On this basis, the patient was given 120,000 rat units of estradiol benzoate in weekly doses of 10,000 units. By November, the lower mass had more than doubled its size, and the entire breast had enlarged. On December 11, at biopsy the neoplasm was called capillary hemangioma. During the ensuing four months there was no active therapy, and the lump continued slowly to increase in size. Quinine hydrochloride and ethyl carbamate (urethane) were then injected into the nodules from May 1936 to July 1936 with little resultant change. The breast, however, became hard and firm. Two weeks after the injections were stopped, the breast began to enlarge rapidly and became painful; a large dark purple area appeared over it. The patient was admitted to the hospital on September 18, and by this time the breast had attained dimensions of 18 by 15 by 10 cm. The nipple was flat, the entire breast was hard, and the skin was stretched and had a red, yellow, and purple mottled appearance. A review of the original biopsy specimen suggested the possibility of hemangioendothelioma. Roentgenograms of the chest revealed no abnormalities. Simple mastectomy was performed on September 30. Prior to operation an interesting finding had been a low blood platelet count; the count returned to normal after operation. In November the patient returned complaining of pain in the shoulders and the back. Shortly thereafter, a nodule was noted in the anterior abdominal wall. Roentgen examination now showed metastatic lesions in the left humerus, the right scapula and the upper lobe of the left lung. The thoracic and cervical vertebrae were normal. Later roentgenograms showed a suggestive lesion in the left scapula, but the spine, the skull, the pelvis and the femurs remained normal. On December 24, she suffered an attack of severe abdominal pain, and ecchymotic areas appeared on the lower extremities. The blood platelets again were found to be at a low

Data on Twenty-Four Cases of Sarcoma of the Breast

Case	Status of Patient *	Age, Years	Symptoms	Operation	Gross Appearance	Microscopic Appearance	Course
				A. ADENOFIBROSARCOMA			
1	Married primipara	33	Tumor for 1 yr. with rapid growth in last 6 mo.; first appeared during lactation	Radical mastectomy	Encapsulated tumor measuring 9 by 7 cm.	Intracanalicular type; poorly cellular; entire mass showed sarcomatous change; few epithelial elements with no hyperplasia; nodes normal	Lost
2	Married	63	Injury followed by tumor which was present for 3½ yr. with more rapid growth in last year; pain	Radical mastectomy	Tumor measured 9 cm. in diameter; lobulated and traversed by clefts into which polypoid masses protruded	Intracanalicular type; sarcomatous change patchy in distribution; no epithelial hyperplasia; slight squamous metaplasia of epithelium; nodes normal	No evidence of disease after 136 mo.
3	Married	49	Lump for 1 mo.; no enlargement; slight tenderness	Local excision	Cyst filled with a polypoid mass measuring 1.5 by 3 cm.	Intracanalicular type; sarcomatous change patchy in distribution; no epithelial hyperplasia	No recurrence after 25 mo.
4	Married primipara	61	Tumor stationary in size for 42 yr.; trauma followed by enlargement 1 mo. before admission	Local excision	Tumor measured 5 cm. in diameter; remnants of fibroadenoma along one side containing foci of calcification	An intracanalicular fibroadenoma with a sarcomatous change in one part; epithelial elements lacking in cellular portion; invasion of adjacent fat	No recurrence after 18 mo.
5	Married	45	Tumor for 1½ yr.	Radical mastectomy	Encapsulated tumor measuring 9 by 12 cm.; cystic	Type of fibroadenoma uncertain; highly cellular; sarcomatous change diffuse; perithelial appearance resulting from necrosis; no epithelial hyperplasia; nodes normal	Lost
6	Single	48	Enlargement and tenderness of the breast for 8 mo.	Radical mastectomy	Cystic tumor measuring 11 by 13 by 16 cm.; excrescences projecting into cysts; some skin fixation	Intracanalicular type; poorly cellular with a diffuse sarcomatous change; no epithelial hyperplasia; nodes normal	Died from pulmonary embolus 11 days after operation; autopsy showed no spread of tumor
7	Married nullipara	52	Enlargement of breast for 6 mo. with more rapid growth in last 2 mo.; intermittent pain	Simple mastectomy	Tumor weighed 10 lb. (4.5 Kg.); cut surface nodular and cystic	Type of fibroadenoma undetermined; poorly cellular; sarcomatous change uniform throughout; no epithelial hyperplasia	No evidence of disease after 19 yr.
8	Single	53	Lump developed after a blow; slow enlargement for 3½ yr.; rapid enlargement for 6 mo.	Simple mastectomy	Tumor measured 6 by 7 by 9 cm.; clefts and cysts with polypoid masses protruding into them; skin adherent	Fibroadenoma of mixed type; poorly cellular; diffuse sarcomatous change; moderate associated epithelial hyperplasia	Died 13 yr. after operation without evidence of recurrence
9	Married nullipara	39	Enlargement of breast for 6 mo.; pain for 1 mo.	Simple mastectomy	Tumor weighed 6½ lb. (3 Kg.); traversed by numerous clefts into which polypoid masses protruded	Fibroadenoma of mixed type; moderately cellular; sarcomatous change uniform throughout; considerable epithelial hyperplasia	No evidence of disease after 8 yr.
10	Single	69	Lump for 6 mo. with steady increase in size; slight pain	Radical mastectomy	Cystic tumor measuring 8 by 10 cm.; skin adherent in places; deposits of calcium	Intracanalicular type; highly cellular with diffuse sarcomatous changes throughout; few epithelial elements; nodes normal	Died 4 yr. after operation from cardiac complications without evidence of recurrence
			Lump for 5 yr., rapid growth for last 5 mo.; slight associated pain	mastectomy	attached to skin; superficial veins dilated; cut surface firm, whorled and nodular	cellular; diffuse sarcomatous change; few epithelial elements; nodes normal	
124		40	Lump for 2 yr. with rapid	Simple	[illegible]	[illegible]	[illegible]

10	Single	69	Lump for 6 mo. with steady increase in size; slight pain	Radical mastectomy	Cystic tumor measuring 8 by 10 cm.; skin adherent in places; deposits of calcium	Intracanalicular type; highly cellular with diffuse sarcomatous changes throughout; few epithelial elements; nodes normal	Died 4 yr. after operation from cardiac complications without evidence of recurrence
11	Married	37	Lump for 2 yr. with rapid growth for last 5 mo.; slight associated pain	Radical mastectomy	Tumor weighing 1,000 Gm.; attached to skin; superficial veins dilated; cut surface firm, whorled and nodular	Intracanalicular type; moderately cellular; diffuse sarcomatous change; few epithelial elements; nodes normal	Lost
12†	.....	40	Lump for 2 yr. with rapid growth for 4 mo.; skin ulcerated	Simple mastectomy	Tumor the size of a grapefruit and adherent to skin	Intracanalicular type; moderately cellular; sarcomatous change uniform throughout; some squamous metaplasia of epithelium	?
13‡	Married	38	Lump for 2 yr.	Radical mastectomy	Circumscribed, firm tumor measuring 4 cm. in diameter traversed by a few clefts	Intracanalicular type; moderately cellular; sarcomatous change diffuse; invasion of adjacent fat; no epithelial hyperplasia; nodes normal	No recurrence after 8 yr.
14§	Married quintipara	39	Nodule for 2 yr. with slow increase in size; rapid enlargement in last 2 mo.; some pain	Simple mastectomy	Encapsulated tumor measuring 10 cm. in diameter; cystic	Apparent pericanalicular type; moderately cellular; sarcomatous change diffuse; epithelial elements widely scattered; foci of cartilaginous metaplasia; cysts a result of necrosis	Lost
15	Married nullipara	34	Lump for 4 yr. with slow increase in size	Local excison	Tumor measured 3 by 4 by 5 cm.; remnants of fibroadenoma at one end; part cystic with polypoid strands projecting into this portion	Hyalinized intracanalicular fibroadenoma with sarcomatous parts; areas with perivascular arrangement; foci of cartilage; squamous metaplasia of epithelium	No recurrence after 6 yr.
				B. FIBROSARCOMA			
16	.....	38	Lump growing rapidly for 9 mo.; pain	Local excision (?)	Tumor measured 7 by 10 cm.; contained a central blood-filled cyst	Well differentiated fibrosarcoma; no epithelial elements	Lost
17	Single	38	Lump with slow increase in size for 11 mo.; some pain; skin red for 1 mo.	Radical mastectomy	Circumscribed, firm tumor measuring 3.5 by 3.5 cm.	Poorly differentiated fibrosarcoma; tumor giant cells present; no epithelial elements; nodes normal	No recurrence after 11 yr.
18	Single	48	Lump for 3 days	Local excision	Firm, circumscribed mass measuring 2 by 2.2 by 3 cm.	Well differentiated fibrosarcoma; focus of osteoid tissue near center; some invasion of surrounding breast; incorporated, atrophic ducts at periphery	No evidence of the disease after 6 yr.
19	Single	30	Lump with steady increase in size for 4 mo.	Radical mastectomy	Moderately soft, circumscribed tumor measuring 3.5 by 4.5 cm.; no adherence to skin or pectoral fascia	Well differentiated; scattered tumor giant cells; a few incorporated ducts at periphery; nodes normal	Local recurrence and distant subcutaneous metastases after 3 yr.; skin nodule showed similar well differentiated growth; patient living after 5 yr. with multiple metastases

* All these patients were women.
† Used by permission of Drs. J. P. Bruckner and L. R. Ferraro, New York.
‡ Used by permission of Dr. Arthur M. Wright, New York.
§ Used by permission of Drs. W. V. Knoll and A. O. Severance, San Antonio, Texas.
‖ Used by permission of Drs. J. C. Ehrlich and Chester Brown, New York.
¶ Used by permission of Drs. T. N. Goodson and A. O. Severance, San Antonio, Texas.
# Used by permission of Dr. S. H. Polayes, New York (Leukemic Tumors of the Breast Mistaken for Lymphosarcoma, Am. J. M. Sc. **143**: 518, 1912).
** Previously reported by C. A. McWilliams and F. M. Hanes.

Data on Twenty-Four Cases of Sarcoma of the Breast—Continued

Case	Status of Patient	Age, Years	Symptoms	Operation	Gross Appearance	Microscopic Appearance	Course
20‖	Married	26	Lump for 1 wk.; patient 3 mo. pregnant	Local excision as lesion was considered a highly cellular fibroadenoma on gross examination	Resilient, ovoid, apparently encapsulated tumor measuring 4 cm. in diameter	Original tumor cells medium sized, rounded or polygonal; little evidence of fibroblastic nature; in recurrence some cells spindle shaped and associated with small amount of collagen; many giant cells; axillary nodes normal	Recurred after 6 mo.; radical mastectomy; died 18 mo. later from metastases to lungs, left femur, pancreas and colon
				C. LYMPHOSARCOMA			
21	Married primipara	22	Incidental mass in breast; admitted for symptoms of a brain tumor	Tumor excised after death	Circumscribed, soft tumor measuring 5.5 cm. in diameter	Medium-sized fairly regular cells arranged in diffuse fashion and supported by a fine reticulin network; some adult lymphocytes at periphery	Patient died after decompression for brain tumor; no tissue removed; no autopsy; relation between two lesions uncertain
22¶	.....	54	Lump for 3 wk.	Radical mastectomy after biopsy	?	Diffuse infiltration of regular medium-sized round cells; cells smaller at periphery and closely resembled adult lymphocytes; no axillary nodes isolated	Postoperative roentgen examination; patient symptom-free after 4 mo.
				D. LEUKEMIA			
23#	.....	25	Lump of uncertain duration	Local excision	Circumscribed ovoid tumor measuring 2.6 cm. in diameter	Medium-sized regular round cells arranged diffusely; some incorporated and atrophic ducts	Lesion thought to be lymphosarcoma; generalized symptoms developed 3 wk. after operation; readmitted 2 mo. later and a blood count then showed acute myeloid leukemia (white blood count = 50,700 with 80% myelocytes); died shortly thereafter
24**	Married primipara	33	Lump for 2 wk.	Local excision—diagnosis: benign lymphoma; recurrence and involvement of opposite breast—bilateral mastectomy	Original tumor circumscribed, firm, pale and homogeneous; it measured 3 cm. in diameter; recurrent nodules similar	Numerous small round cells slightly larger than adult lymphocytes; infiltration most dense in lobules; axillary nodes involved	No blood count until after second operation; white blood count then 117,000 with 90% lymphocytes; died about 2 mo. after [illegible] of

level (51,000). The abdominal symptoms were believed to be due to hemorrhage, as she soon passed into a state of shock. She died the following day. The entire course of the disease was thus about twenty-one months. Radiotherapy was given to the shoulders and the abdominal mass without appreciable benefit.

Biopsy (fig. 15) showed numerous variously sized anastomosing vascular spaces lined by a single layer of fairly uniform medium-sized endothelial cells. Some of the spaces contained blood; others were empty. The vessel walls were composed of a thin layer of hyalinized fibrous tissue. Although the lesion was

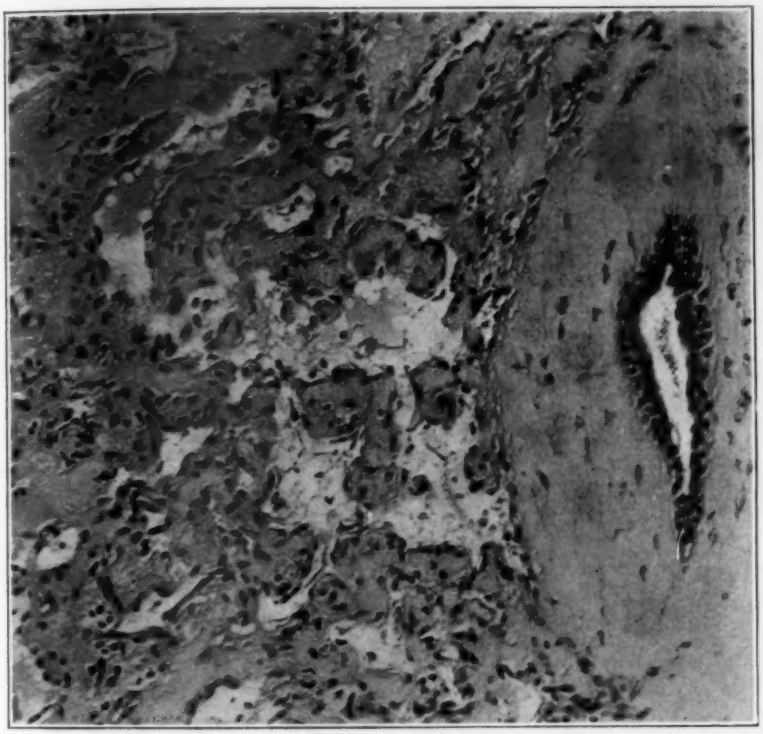

Fig. 15 (case 25).—Malignant hemangioendothelioma. The original biopsy specimen, showing the resemblance of the tumor to capillary hemangioma. There is little to suggest its malignant nature.

fairly well circumscribed, there was extension into the surrounding fat in one place.

The breast on removal weighed 1,647 Gm. When sectioned, it contained more than a liter of clotted and unclotted blood. Grossly, the cut surface appeared as a delicate spongy meshwork of numerous thin-walled large and small cavities.

There was a striking change from the findings of the original biopsy. Numerous irregular spaces were seen lined by large cells several layers thick so that sometimes the clefts were almost completely filled (fig. 16). The individual cell was

large, somewhat irregular, hyperchromatic and elongated with a deep-stained oval nucleus which sometimes contained one or more prominent nucleoli. Mitoses averaged about 1 per high power field. In the more cellular and compact areas, the cells had a roughly polygonal shape. Occasional foci were noted where the tumor resembled the biopsy specimen. There were extensive infiltration and almost complete replacement of the breast tissue. The vessels had anastomosed widely and often formed fairly extensive pools and lakes.

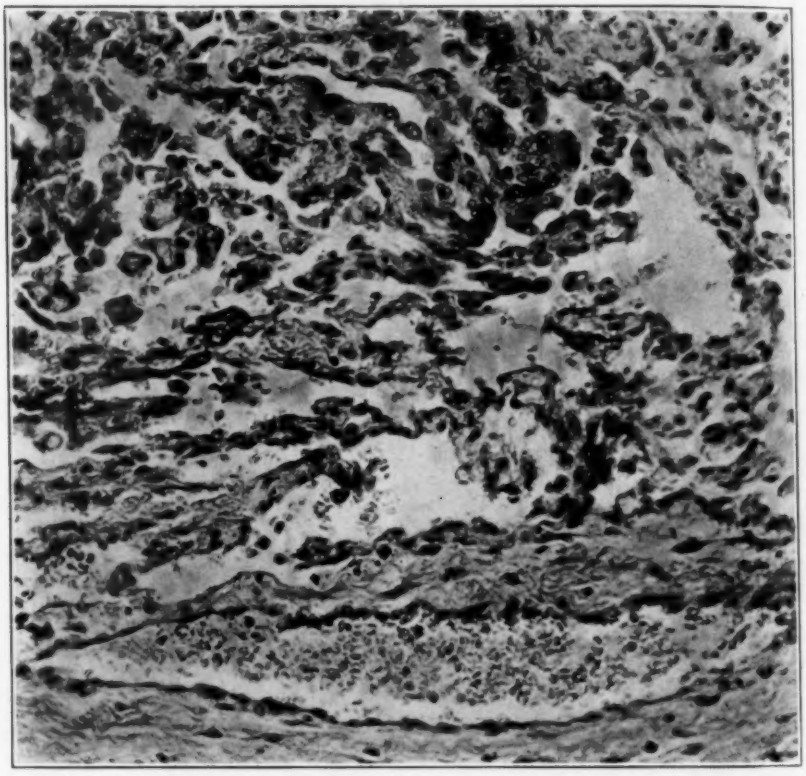

Fig. 16 (case 25).—Malignant hemangioendothelioma. The appearance of the lesion after amputation is shown. The tumor is now more cellular, and the cells lining the anastomosing vessels are piled-up, large and irregular.

CASE 26.[41]—A white woman, a widow 65 years of age, was admitted to the Memorial Hospital, Worcester, Mass., with a lump in the right breast. The symptoms had begun two weeks before with a stinging sensation in this breast followed soon after by the appearance of the nodule, rapid enlargement of the entire structure and purple discoloration of the overlying skin. There was some associated pain.

41. Used with the permission of Drs. Walter C. Seelye and James P. Beck, Worcester, Mass.

Physical examination revealed a mass the size of a golf ball 2 inches (5 cm.) lateral to the nipple with elevation of the overlying skin. The skin over the mass had a reddish purple hue, while the surrounding skin was slightly discolored and had a faint pigskin appearance. On palpation a mass about half the size of a grapefruit was felt in the substance of the breast in the vicinity of the elevated area. Roentgenograms of the chest revealed no abnormalities.

Radical mastectomy was performed, and one month later recurrent lesions developed in the scar. Roentgenograms now showed metastatic lesions in the lungs. Treatment of the recurrence and the metastases by irradiation had no effect. The patient became rapidly worse, and death occurred about two months after the onset of symptoms.

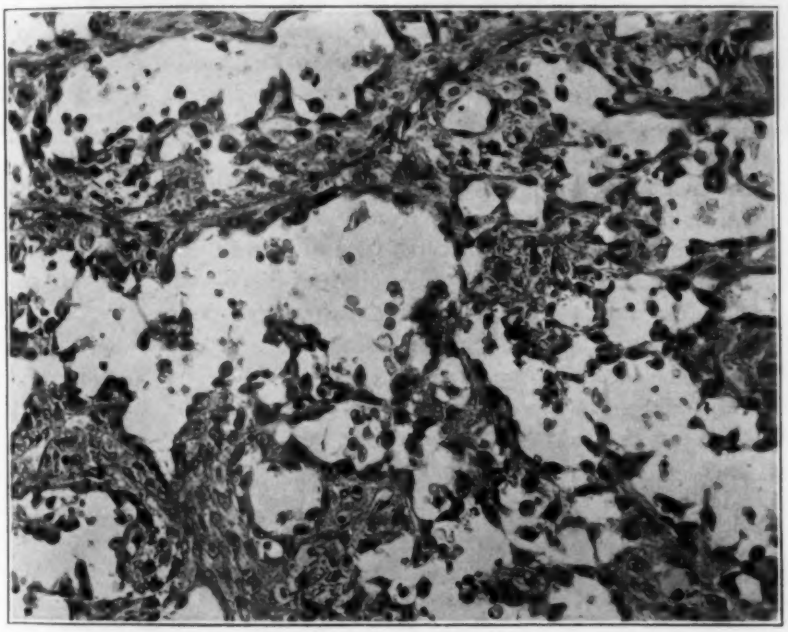

Fig. 17 (case 26).—Malignant hemangioendothelioma. The numerous, irregular anastomosing blood vessels are lined by large hyperchromatic cells which are sometimes piled up. Similar cells are found in the stroma.

Gross examination of the breast showed a large semifirm mass in the upper outer quadrant with elevation and thinning of the overlying skin. The nipple was retracted, and the skin over the entire outer half was blue. The tumor measured about 8 by 5 cm. Its cut surface was grayish white and semitranslucent and contained numerous small yellow opaque foci and areas of hemorrhage. Near the center was an irregular cavity filled with clotted blood.

Microscopically the breast was almost entirely replaced by large elongated hyperchromatic tumor cells arranged in indefinite vascular structures (fig. 17). The cells lining the channels varied from one to several layers thick. Some of the clefts contained a small amount of blood. The vessels were supported by a small amount of fibrous stroma, which was infiltrated by the tumor cells. Mitoses

averaged 2 to 5 per high power field. Foci of necrosis were present, and only a few mammary ducts remained. The overlying skin was ulcerated and intimately adherent to the growth. The axillary lymph nodes were normal.

LIPOSARCOMA AND MYOSARCOMA

Lifvendahl [42] and Fox reported examples of liposarcoma appearing in the female mammary gland. Neal recorded a similar tumor occurring in the male breast. The relation to lipoma is uncertain.

Dretzka [43] described a breast tumor thought to be leiomyosarcoma. Bérard, Martin and Henry [44] observed a tumor which was called myosarcoma, and it seems likely that this neoplasm was of smooth muscle derivation. Isidor [45] mentioned a malignant tumor diagnosed as leiomyoma and believed to have arisen from the wall of a small artery. Neal found leiomyosarcoma involving the male breast. This diagnosis should be made on the presence of myofibrils and not on any superficial resemblance to muscle fibers.

Sailer observed what was undoubtedly rhabdomyosarcoma in the substance of the breast, and no connection with the pectoral muscles could be demonstrated. Leroux and Chaton [46] and Billroth noted striated muscle fibers in breast tumors. The source of this tissue is undetermined; perhaps these tumors represent teratomatous growths.

There are too few of these cases from which to draw conclusions other than that they seem to exhibit a rather high degree of malignancy. The clinical findings are much the same as for fibrosarcoma, and the differentiation can be made only by histologic means.

There have been no examples of these neoplasms observed in this laboratory.

MIXED TUMOR

The term "mixed tumor" has been used not specifically to limit but to simplify the discussion of the mammary neoplasm which contains two or more different tissues. We do not mean to convey the idea that every such growth should be designated simply as a mixed tumor; whenever possible, it should be classified according to the probable manner

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42. Lifvendahl, R. A.: Liposarcoma of the Mammary Gland, Surg., Gynec. & Obst. **50**:81, 1930.

43. Dretzka, L.: An Unusual Recurrent Mammary Tumor, with Pathological Opinions, Am. J. Surg. **7**:693, 1929.

44. Bérard, L.; Martin, J. F., and Henry, M.: A propos d'un cas de myosarcome mammaire, Lyon chir. **34**:602, 1937.

45. Isidor, P.: Essai d'étude critique des sarcomes du sein, Gynécologie **33**:382, 1934.

46. Leroux, R., and Chaton, M.: Dysembryome complexe de la glande mammaire, Bull. Assoc. franç. p. l'étude du cancer **22**:80, 1933.

of its development. A malignant tumor of this nature is found both with and without malignant epithelial elements. Carcinosarcoma constitutes the first type, while malignant teratoma and fibrosarcoma or adenofibrosarcoma with osteoid or cartilaginous metaplasia belong to the second.

Cases of mammary neoplasm with foci of bone or cartilage or both have occasionally been recorded in the literature. Apparently the first reported was that of Bonet.[47] In 1937, Raso [48] was able to collect 74 cases and to add 1 of his own.

The source of the osteoid and cartilaginous elements has long been a subject of debate. Two explanations have been offered: (1) the theory of embryonic inclusion and (2) the theory of metaplasia.

The first view, in accordance with Cohnheim's theory, has been advocated by St. Arnold,[48a] Wilms,[49] Lecène,[50] Hueter and Karrenstein,[51] Dyke [52] and others. St. Arnold suggested that a mixed tumor is a product of aberrant blastomeric inclusions from the developing thoracic skeleton and specifically from the region of the clavicle. This idea is dependent entirely on the concept of the specificity of the germ layers, a belief no longer considered tenable. Another view is that a mixed tumor is a result of misplacement of embryonic totipotential cells, a true teratoma. This possibility was demonstrated by the observance of teeth and a dental process in a mammary tumor by McIver [53] and of rudimentary hair follicles in another by Gioia and Bianchi,[54] structures which can be explained satisfactorily in no other way. Thus, malignant and one-sided deviation of one of the elements in such a tumor could lead to sarcoma or to carcinoma in which other structures would be found.

47. Bonet, T.: Mammae osseae in virgine cum pectoris hydrope, in Sepulchretum sive anatomia practica ex cadaveribus morbo denatis, Geneva, Cramer & Perachon, 1700, vol. 2, p. 522.

48. Raso, M.: I Chondroosteomi e i condroosteosarcoma della mammella umana, Pathologica **29**:229, 1937.

48a. St. Arnold: Ueber einem knorpel- und knochenhaltigen Tumor der Brustdrüse, Virchows Arch. f. path. Anat. **148**:449, 1897.

49. Wilms, M.: Mischgeschwülste der Brustdrüse, in Die Mischgeschwülste, Leipzig, A. Georgi, 1902, vol. 3, p. 169.

50. Lecène, P.: Les tumeurs mixtes du sein, Rev. de chir., Paris **33**:434, 1906.

51. Hueter, C., and Karrenstein: Eine Mischgeschwülst (Osteoidsarkom) der weiblichen Milchdrüse, Virchows Arch. f. path. Anat. **183**:495, 1906.

52. Dyke, S. C.: A Bony Tumour of the Breast, Brit. J. Surg. **14**:323, 1926.

53. McIver, A. M.: Teratoid Mixed Tumors of the Breast, Ann. Surg. **77**: 354, 1923.

54. Gioia, T., and Bianchi, A. E.: Tumor mixto de la glándula mamaria en el hombre, Bol. y trab. Soc. de cir. de Buenos Aires **14**:146, 1930.

Kreibig [55] reported a neoplasm containing foci of carcinoma, sarcoma, cartilage and osteoid tissue. In addition, a small fibroma and a hemangioma were associated, and he considered the lesion a malignant hamartoma. As a general rule, however, it seems unnecessary to explain the vast majority of these tumors on the basis of teratoma, and this possibility should be reserved for those explainable by no other means.

The metaplastic theory offers by far the best solution of the problem and has been supported by Stilling,[56] von Hacker,[57] Sehrt,[58] Deaver and McFarland, Thinnes,[59] Fry,[60] Ewing and Tudhope.[61] The number of its exponents has increased greatly in recent years so that it is now the generally accepted explanation.

There are several reasons why this hypothesis seems more likely to be correct. It is not unusual to find definite stages of transition between the fibrous tissue of a tumor and its cartilaginous or osseous foci, an observation which formed the principal basis for the acceptance of the theory by the earlier writers. The frequent occurrence of bone or cartilage-containing tumors in the breasts of dogs is suggestive in that it seems somewhat far fetched to suppose that these animals are so much more prone to embryonic rests than human beings. The occasional presence of these elements in transplanted tumors of animals has been perhaps the most convincing evidence. Haagensen and Prime [62] have several times noted the development of such tissues in the stroma of transplanted carcinomas of mice at the Cancer Research Laboratories of Columbia University. Further transplantations of these tumors, presumably not including the cartilaginous or osseous portions, have resulted in the sporadic appearance of these tissues. Foulds [63] obtained similar results with transplanted adenocarcinoma of the oviduct of a domestic

55. Kreibig, W.: Zur Kenntnis seltener Geschwulstformen der weiblichen Brustdrüse, Virchows Arch. f. path. Anat. **256**:649, 1925.

56. Stilling, H.: Ueber Osteoidsarkome der weiblichen Brustdrüse, Deutsche Ztschr. f. Chir. **15**:247, 1881.

57. von Hacker, V. R.: Ueber das Vorkommen von Knorpel und Knochen in einer Geschwulst der weiblichen Brustdrüse, Arch. f. klin. Chir. **27**:614, 1881-1882.

58. Sehrt, E.: Beiträge zur Pathologie der Milchdrüse, Beitr. z. klin. Chir. **55**:575, 1907.

59. Thinnes, H.: Ueber einem Fall von Chondrosarkom der weiblichen Brustdrüse, Virchows Arch. f. path. Anat. **264**:150, 1927.

60. Fry, H. J. B.: Osteoclastoma (Myeloid Sarcoma) of the Human Female Breast, J. Path. & Bact. **30**:529, 1927.

61. Tudhope, G. R.: A Complex Malignant Mammary Tumour, J. Path. & Bact. **48**:409, 1939.

62. Haagensen, C. D., and Prime, F. C.: The Spontaneous and Transplantable Tumors of Small Laboratory Animals, unpublished data.

63. Foulds, L.: A Transplantable Carcinoma of a Domestic Fowl, with a Discussion of the Histogenesis of Mixed Tumours, J. Path. & Bact. **44**:1, 1937.

fowl. Dunning, Bullock and Curtis [64] were able to produce osteochondrosarcoma in the mammary glands of rats with the injection of a solution of 3,4-benzpyrene, and so it would seem that bone and cartilage can be produced by fibrous tissue provided the local environmental conditions are right. Another factor against the specificity of the germ layers and the necessity of invoking fetal rests to explain a mixture of tissues is the modern concept of the possibility of cartilage formation by epithelial cells.[65]

Therefore, it is probable that the presence of cartilage and bone in mammary tumors can usually be considered a metaplastic process, although of course some of the more complex and bizarre forms may have a teratomatous origin. Accordingly, it may be assumed that in most instances the primary lesion is fibroblastic in nature and that the osseous or cartilaginous change occurs secondarily. In many of the reports of cases the statement is made that the tumor resembled fibrosarcoma at its periphery, while the other elements were confined chiefly to the more central portions. That fibrosarcoma is the primary change has been suggested also by Isidor. For this reason, it is more accurate to speak of these neoplasms as fibrosarcoma with osteoid or cartilaginous metaplasia than as osteoid sarcoma or chondrosarcoma.

The clinical behavior is much the same as that of fibrosarcoma. How often metastatic foci produce bone or cartilage is uncertain since satisfactory data for the determination of this feature are lacking. That these foci may do so on occasion is demonstrated by the observance of cartilage in a secondary lesion by Raso and of osteoid tissue in metastatic deposits by Stilling. A somewhat analogous situation is the sporadic production of cartilage by certain transplanted tumors.

In the interpretation of the second class of malignant mixed tumors, i. e., composed of both sarcomatous and carcinomatous parts, carcinosarcoma, the same problems arise. The degree to which cancer cells can assume a spindle shape has been appreciated only in recent years as a result of the study of transplanted carcinoma in animals. This has definitely demonstrated that the mere spindle cell character of tumor cells cannot be considered sufficient evidence that the neoplasm is sarcoma. Hence, it appears likely that in many of the older reports supposed carcinosarcoma was really pure carcinoma. The fact that many of them recurred or metastasized as carcinoma suggests this conclusion. To be certain of the presence of both tumor elements, there should be metastases of both types, a criterion which is seldom found.

64. Dunning, W. F.; Curtis, M. R., and Bullock, F. D.: The Respective Roles of Heredity and Somatic Mutation on the Origin of Malignancy, Am. J. Cancer **28**:681, 1936.

65. Allen, A. C.: So-Called Mixed Tumors of the Mammary Gland of Dog and Man, Arch. Path. **29**:589 (May) 1940.

True combined carcinoma and sarcoma develops in three possible ways:

1. It may be true teratoma, and a malignant transformation of both epithelial and mesodermal tissues could produce such a growth. This constitutes the combination tumor of Meyer.[66]

2. It is believed that carcinoma may sometimes incite its stroma to a sarcomatous proliferation. In this way, the composition tumor of Meyer or the carcinoma sarcomatodes of Takano [67] results. The reverse possibility is also true, namely, that surrounding epithelial elements may be stimulated to malignant proliferation by preexisting sarcoma. The observance of a sarcomatous change in the stroma of transplanted carcinoma in animals by Apolant,[68] Haaland,[69] Russell [70] and Haagensen and Prime suggests this possible mode of development. Further, Russell was able to take such mixed tumors, transplant their separate components and obtain a pure growth of each type. The supposed development of carcinoma during the propagation of sarcoma was noted by Nicholson.[71]

3. The same irritant may lead to the simultaneous reaction of both tissues; this is indicated by the appearance of similar growths in irradiated skins and in the subcutaneous tissues of rats by the injection of a solution of 3,4-benzpyrene.[64] Likewise, carcinoma and sarcoma may develop at the same time in the breast but in different regions and by continued growth subsequently coalesce. This was termed collision tumor by Meyer, and reputed examples have been reported by Schlagenhaufer,[72] Kettle,[73] Kennedy and Case [74] and Curphy.[75]

Three of our tumors contained osteoid or cartilaginous tissue. In all there were transition stages between the fibrous tissue component

66. Meyer, R.: Beitrag zur Verständigung über die Namengebung in der Geschwulstlehre, Zentralbl. f. allg. Path. u. path. Anat. **30**:291, 1919.

67. Takano, N.: Ueber das Carcinoma sarcomatodes der Mamma, Arch. f. klin. Chir. **103**:154, 1914.

68. Apolant, H.: Die epithelialen Geschwülste der Maus, Arb. a. d. k. Inst. f. exper. Therap. zu Frankfurt a.M. **1**:11, 1906.

69. Haaland, M.: Contributions to the Study of the Development of Sarcoma Under Experimental Conditions, Scient. Rep. Imp. Cancer Research Fund **3**:175, 1908.

70. Russell, B. R. G.: Sarcoma Development Occurring During the Propagation of a Hemorrhagic Adenocarcinoma of the Mamma of the Mouse, J. Path. & Bact. **14**:345, 1910.

71. Nicholson, G. W.: A Small Carcinoma in Association with a Transplanted Sarcoma in a Rat, J. Path. & Bact. **16**:518, 1911.

72. Schlagenhaufer, A.: Carcinom und Riesenzellsarkom derselben Mamma, Centralbl. f. allg. Path. u. path. Anat. **17**:385, 1906.

73. Kettle, E. H.: Carcinoma and Sarcoma of the Breast, Lancet **2**:750, 1912.

74. Kennedy, J. W., and Case, E. A.: Sarcoma and Carcinoma of the Same Mammary Gland, Proc. Path. Soc. Philadelphia **18**:40, 1916.

75. Curphy, W. C.: Primary Spindle Cell Sarcoma Associated with a Primary Scirrhous Carcinoma, J. Kansas M. Soc. **36**:412, 1935.

and the cartilage or bone. The osteoid tissue was found near the center of a tumor which was unquestionably fibrosarcoma, while the 2 cartilage-containing neoplasms were adenosarcoma. One of the latter showed cartilage both in the actively growing part and in the remnants of old hyalinized fibroadenoma. Similar changes have been noted also in fibroadenoma. We were permitted to review the sections from another tumor (Bernhard [76]); these showed more extensive formation of osteoid elements, but again there was unmistakable evidence in places that the tumor was fibrosarcoma with extensive metaplasia. Dr. M. N. Richter of the New York Post-Graduate Medical School and Hospital showed us a section of a tumor which histologically resembled true osteogenic sarcoma, and from this section alone it was impossible to differentiate it from one. Unfortunately, it was an old case, and we do not know what additional microscopic preparations from other parts of the tumor might have revealed.

There were 2 tumors which may have been carcinosarcoma. In both there were nests of malignant epithelial cells separated by extensive bands of spindle cells suggestive of sarcoma. In 1 of them, formation of cartilage also had taken place. Since it is not within the scope of this paper to include any tumor with malignant epithelial elements, a detailed discussion of these 2 tumors is omitted; they have been mentioned only to complete the series.

SUMMARY

Breast sarcoma has been reviewed, and the diverse forms have been separated into fairly well defined groups according to histogenesis. The advantage of such a division becomes apparent when the prognosis is considered.

Adenofibrosarcoma constitutes a rather specific type of breast tumor and represents a sarcomatous transformation of fibroadenoma. It is the most frequently encountered variety and is usually clinically benign. On the other hand, true fibrosarcoma arising from the ordinary connective tissue of the breast has the same malignant potentialities as similar tumors in other regions.

It is believed that the presence of cartilage or bone in a breast tumor is usually a result of metaplasia in fibrosarcoma or adenofibrosarcoma and does not necessarily imply a teratomatous origin.

Myosarcoma, liposarcoma, malignant hemangioendothelioma and lymphoblastoma are interesting but unusual neoplasms which generally pursue a relatively rapid and unfavorable course.

Other terms often employed in the discussion of mammary sarcoma merely confuse further an already complicated subject and serve no practical purpose.

76. Bernhard, W. G.: To be published.

ECHINOCOCCOSIS OF THE BREAST

REPORT OF A CASE

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Echinococcosis may be localized anywhere in the body, but the breast is a rare location. In 1923, Escudero [1] made a complete review of the publications of cases echinococcosis of the breast, and since then few cases have been reported. Roldán [2] reported 1 case; Bussalay,[3] 1; Pasman and Mosto,[4] 1; Chifflet and Ardao,[5] 2, and Charlone and Sacco-Ferraro,[6] 1. Canavero [7] published the report of a case of echinococcosis alveolaris of the breast.

The diagnosis of echinococcosis was made before operation in a few cases; commonly the diagnosis was made after operation. When Casoni's test of the skin and the Ghedini complement fixation test are positive and eosinophilia is present or when a puncture of the tumor gives clear fluid, the diagnosis of echinococcosis is easily made. Until now there has been no information about roentgen diagnosis of echinococcosis of the breast.

REPORT OF CASE

Mrs. E. C., a white married woman 24 years old born in Argentina, was admitted to the Centro de Investigaciones Tisiológicas in November 1940 com-

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From the Centro de Investigaciones Tisiológicas, Prof. R. Izzo, Director.

1. Escudero, P.: Bibliografía de la hidatidosis: VI. Hidatidosis de las mamas, Actas y trab. d. segundo Cong. nac. de med. argent. **1**:558, 1923.
2. Roldán, A.: Quistes hidáticos, An. Fac. de med. de Montevideo **10**:291, 1925.
3. Bussalay, E.: Voluminosa cisti di echinococco della mamella. Estirpazione. Guarigione, Policlinico (sez. prat.) **5**:1779, 1927.
4. Pasman, F. R., and Mosto, D.: Quiste hidatídico de mama, Prensa méd. argent. **16**:1545, 1930.
5. Chifflet, A., and Ardao, H.: Quiste hidático de seno, An. Fac. de med. de Montevideo **20**:365, 1935.
6. Charlone, R., and Sacco-Ferraro, L.: Quiste hidático de la mama, Arch. urug. de med., cir. y especialid. **10**:607, 1937.
7. Canavero, M.: Su di una rara localizzazione dell' echinococco alveolare alla ghiandola mammaria, Ann. ital. di chir. **10**:566, 1931.

plaining of a tumor in the left breast which had been observed approximately three months before and which had progressively increased in size until admission. She had had no pain and no loss of weight.

Past History.—She was born in Pergamino, Province of Buenos Aires, and had had two sons and four abortions.

Physical Examination.—Physical examination revealed a fairly well developed white woman in good general condition. The temperature was normal; the pulse rate was 75; the blood pressure was 130 systolic and 85 diastolic. There was a tumor in the upper external quadrant of the left breast. Its surface was smooth, and it was about 5 cm. in diameter. It was renitent and gave the impression of a solid tumor not adherent to either the skin or the pectoralis muscles. The skin above the tumor was normal, and no infiltration could be felt around it. The

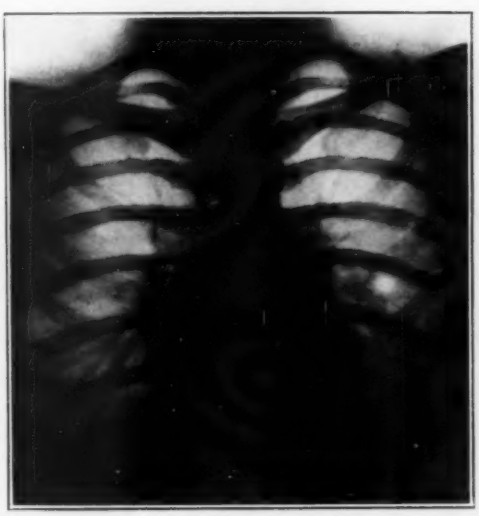

Fig. 1.—Roentgenogram showing the patient's normal chest.

examination was not painful, and it was easy to displace the tumor with the mammary gland. No lymph nodes were felt in the supraclavicular region or in the axilla. A roentgenogram showed a normal chest (fig. 1). The diagnosis was benign tumor of the breast (adenoma or adenofibroma), and operation was advised.

Operation.—On November 8, with local anesthesia induced with procaine hydrochloride, a radial incision was made in the breast, and an echinococcic cyst was found. An incision of 5 cm. was made in the adventitia, and the membrane of the parasite was completely removed. The inner surface of the adventitia was painted with a 10 per cent solution of formaldehyde; then the incision in the adventitia was closed with a continuous suture of catgut. The wound was closed in layers with catgut.

Progress.—The wound healed by primary intention (fig. 2). Two days later, examination of the blood showed 5,400 white cells and 7 per cent eosinophils. Seven days later, the complement fixation test was still negative.

Pathologic Report (Dr. L. Irigoyen).—The specimen was a cyst with whitish flexible walls which contained transparent fluid (fig. 3).

Microscopic Description: The wall of the cyst did not have any tissue structure. It consisted of two parts: the outer (cuticular) part, which was formed of

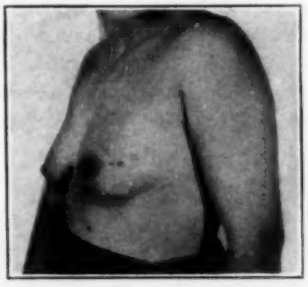

Fig. 2.—The scar seven days after operation.

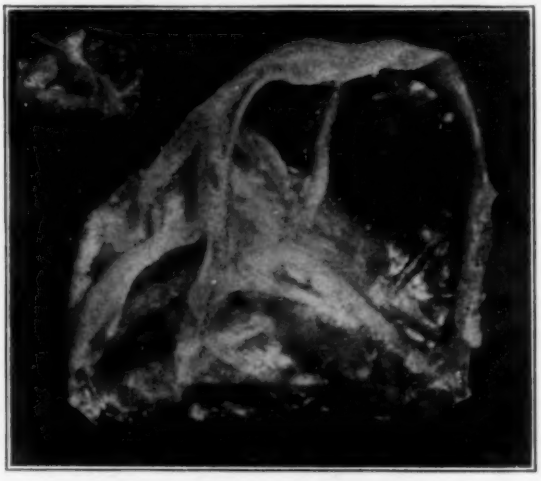

Fig. 3.—The membrane of the parasite.

many layers, and the inner (germinative) part, which contained grains which, when enlarged, showed some scolices. The diagnosis was echinococcic cyst.

COMMENT

In our patient, who was born and grew up in a place where echinococcic cyst is common, the most important features were: a slow increase in the size of the tumor, a smooth surface and a great mobility.

The treatment in many cases has consisted of partial resection of the breast, including the parasite, the adventitia and portions of the mammary gland. It is not necessary to remove any part of the mammary gland unless there is severe chronic infected mastitis. We believe that the best procedure is the application of Posadas' technic [8] performed in our case: complete evacuation of the parasite, dabbing the inner surface of the adventitia with solution of formaldehyde and complete closure of the wound.

8. Posadas, A.: Traitement des kystes hydatiques, Rev. de chir. **19**:374, 1899.

MOTILITY AND RESPONSE OF THE GREAT OMENTUM

I. FLUOROSCOPIC OBSERVATIONS ON OMENTAL ACTIVITY OF DOGS

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There have been innumerable speculations on the functions and activity of the great omentum. Theories have varied from that of Erisistratus,[1] who centuries ago claimed the structure had no function, to those of modern writers who speak of the "intelligence" of the omentum. And even today, a survey of the medical literature shows that many different opinions are held concerning the physiology of this structure.

Almost all students are informed that the omentum is the "great protector of the abdomen" which by some strange inherent power seeks out and tries to arrest trouble. However, extensive experience with abdominal operations for intraperitoneal suppuration has repeatedly demonstrated that the omentum is indeed capricious in its response to such calls of duty. The observations reported here are the first in a series of studies which will attempt to clarify the problem of omental activity and response. Additional experiments are being conducted to determine the extent of chemotactic and phagocytic response, secretory and absorptive function and the ability of omental grafts to survive.

It is a matter of common medical knowlerge that the omentum is often found adherent to inflamed structures within the peritoneal cavity. In 1896, Stichler [2] introduced small nails into the peritoneal cavity of dogs and observed that they were walled off by the omentum. In 1899, Milran,[3] after a series of experiments on various laboratory animals, concluded that the omentum was endowed with motility and that this motility was longitudinal, transverse and about the axis of the omentum itself.

While all writers on the subject agree that the great omentum has motility, they are divided into two schools concerning the mechanism

From the Departments of Research Surgery and Laboratories, Jewish Hospital.

1. Erisistratus, cited by Hertzler, A. E.: The Peritoneum, S. Louis, C. V. Mosby Company, 1919, vol. 1.

2. Stichler, cited by Siciliani.[6]

3. Milran, cited by Siciliani.[6]

of its ability to travel from place to place. The theory of intrinsic omental motility was most vigorously championed by Rutherford Morison,[4] Saint and Dunelm[5] and Siciliani.[6] Morison spoke of the great omentum as the "policeman of the abdomen" that travels about with considerable activity and is attracted by some sort of information to neighborhoods in which mischief is brewing. He likened these movements to those of a jellyfish. Siciliani expressed the opinion that the omentum has active power of movement, and while he did not state what the origin of the motility is, he suggested that it may be due to its "histological structure and biological properties."

In 1906, Fisher[7] expressed the opinion that the great omentum does not have intrinsic motility. Wilkie[8] and Adams[9] also opposed the concept of active omental motility and explained the excursions as being produced by peristalsis. Normally, the peristaltic movements of the small intestine keep the great omentum spread uniformly over the surface of the intestine. When local inflammation involves the peritoneal covering of a few coils of the small intestine, the movements of these coils are restrained. This inactivity of the intestine produces a quiescent area, and the great omentum is pushed by actively moving coils of intestine toward this quiescent region. When the omentum eventually comes in contact with the inflamed area, it becomes involved in the inflammatory process itself. The inflammation produces adhesions between the omentum and the bowel and thereby tends to limit the spread of the infection.

Except for the work of Florey, Walker and Carleton[10] in 1926 and of Siciliani in 1932, little experimental investigation has been carried out in recent years that added to the knowledge of this subject. Indeed, Johnson[11] in 1930 stated that no one knows or has proved what the automotive power of the great omentum may be. However, in justice to Florey, Walker and Carleton, it should be said that they built up a strong case in favor of the theory of passive motility. Their experiments led them to believe that the movements of the great omentum in the cat, the rabbit and the mouse were purely passive.

4. Morison, R.: An Introduction to Surgery, Bristol, England, John Wright & Sons, 1910.

5. Saint, C. F. M., and Dunelm, M. S.: Clin. J. **44**:172, 1915.

6. Siciliani, G.: Folia med. **18**:949, 1932.

7. Fisher, T.: Brit. M. J. **2**:1329, 1911.

8. Wilkie, D. P. D.: Brit. M. J. **2**:1103, 1911.

9. Adams, S. E.: Lancet **1**:663, 1913.

10. Florey, H.; Walker, J. L., and Carleton, H. M.: J. Path. & Bact. **29**:97, 1926.

11. Draper, J. W., and Johnson, R. K.: Tr. Am. Gastro-Enterol. A. **33**:30, 1930.

According to these investigators, the factors involved are: (1) posture, (2) peristalsis and (3) diaphragmatic excursions.

In 1913, Adams observed omental movements fluoroscopically, but his work has been criticized because he used lead shots as opaque bodies. Saint and Dunelm expressed the belief that these lead shots added appreciable weight to the free border of the omentum and consequently inhibited its motility. Florey's work of direct observation of omental activity by means of windows in the wall of the abdomen is open to the criticism that artificial conditions prevailed which might have altered omental response.

EXPERIMENTAL DATA

Our studies were directed toward the observation of omental motility and response under conditions as near to normal as possible. Through high midepigastric incisions, various opaque bodies were sutured into the free border of the great omentum of 4 dogs. The high incision was chosen to avoid postoperative adhesions between the parietal peritoneum and the free portion of the omentum. Silver brain clips were buried with an inverting suture into the free edge of the omentum of 2 dogs; Michel clips were used for a third dog, and leaded glass thread was the material used for a fourth animal. All of these opaque bodies were so small and light that their size and weight could not possibly be appreciable factors in influencing motility or response of the great omentum.

EXPERIMENT 1.—The dog was a white female fox terrier, weighing 7 Kg. With the dog under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midepigastric incision 4 cm. long was made, and the great omentum was brought out of the wound. The omentum was thin and semimembranous, measuring 15 cm. from the greater curvature of the stomach to its free edge on the right side and 12 cm. along the left border. An open Michel clip was buried in the lowermost dependent portion of the right side by means of an inverting black silk suture. Similarly, a closed Michel clip was sutured into a corresponding position on the left side. The great omentum was carefully replaced in the abdominal cavity, and the wound was closed in layers.

Three weeks later, the animal was examined under the fluoroscope in the supine position. Its legs were firmly held by two assistants, and within a few moments the animal lay quiet and passive. The clips were seen to move up and down with respirations, closely following the diaphragmatic excursions. The range of movement was approximately 1 cm. No lateral or axial movements were noted despite repeated observations extending over a period of about one-half hour. The dog was then given 1.5 cc. of a 1:2,000 solution of prostigmine methylsulfate intramuscularly. Several minutes later exceedingly active peristalsis was noted, evidenced by the rapid progression of gas bubbles within the bowel. At the height of peristaltic activity the left clip ascended and approached the right clip, which remained relatively immobile in the right upper quadrant of the abdomen. Five minutes later, the animal vomited and immediately thereafter was placed under the fluoroscope. No omental movement was seen. Shortly afterward, the dog defecated and was again viewed under the fluoroscope, but no omental excursions were made out.

Two weeks later, the experiments were repeated with exactly similar results. After the effect of the prostigmine methylsulfate was allowed to wear off, a sterile

5 cm., 22 gage needle was inserted into the right lower quadrant of the abdomen, at the level of the lowermost extent of the omentum on the opposite side of the abdomen. The right clip was located about 4 cm. above the level at which the needle was introduced. This point was chosen in order to see whether the right clip would descend or the left clip would move transversely in response to the irritation of the foreign body. No omental response, as indicated by a change of position, was noted over a period of some fifteen minutes despite manipulation of the needle in all directions (see illustration).

The clips are in the free border of the dog's great omentum, and the sterile needle has been introduced into the peritoneal cavity. A similar site was chosen for the inoculation of B. coli. This area is well within reach of the omentum.

One month later, 0.5 cc. of a fresh virulent culture of Bacillus coli containing 6,000,000,000 organisms per cubic centimeter was injected into the peritoneal cavity of the right lower quadrant of the abdomen. Six hours later, the animal was observed under the fluoroscope, and the clips were seen to be in their former positions nowhere near the site of the implantation of bacteria. This procedure was repeated two weeks later when 1 cc. of a heavy suspension in a solution of sodium chloride of purulent material obtained from the lumen of a suppurating appendix was injected intraperitoneally into the right lower quadrant of the abdomen. B. coli was subsequently cultured from this suspension. Twenty-six

hours later, the animal was examined under the fluoroscope, but no change in omental position was observed.

Because of the failure of the omentum to respond to either the insertion of a needle or the implantations of bacteria, it was thought that adhesions might have formed after the original laparotomy, thus restraining all omental activity. Exploratory laparotomy was therefore performed through a left midrectus incision. No adhesions were found within the abdominal cavity, nor was there any evidence of previous peritonitis. The clips were located and found to be completely encapsulated. The free edge of the omentum was entirely mobile, and except for slight induration about the clips, there was no evidence that any changes had occurred as a result of the original operation for their insertion.

EXPERIMENT 2.—The dog was a black male mongrel and weighed 9.4 Kg. With the animal under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midepigastric incision 4 cm. long was made, and the great omentum was brought out of the wound. It was moderately fatty, measuring 8.5 cm. from the greater curvature of the stomach downward to its free border along the right side, 6 cm. along the left side and 14 cm. in its midportion. Two strands of leaded glass silk were buried in the free edge of the midportion of the most dependent part, and one strand was buried in the right and left extremities of the omentum, respectively. The abdomen was closed in layers after the omentum had been carefully reposited.

Three weeks later, the animal was examined under the fluoroscope. The leaded glass silk was seen to move up and down synchronously with respiration, within an excursion of approximately 1 cm. No lateral or axial movements were observed. After a period of study of about one-half hour, during which no changes in the type of omental mobility were perceived, the dog was given 1.5 cc. of a 1:2,000 solution of prostigmine methylsulfate by intramuscular injection. Ten minutes later, active intestinal peristalsis became clearly visible, and the right free border of the omentum was seen to approach the midline. The distance between the strands of silk decreased markedly. During the examination, the dog defecated, but this did not appear to influence the movements of the omentum.

Two weeks later, the procedure was repeated with similar results. When the effects of prostigmine methylsulfate had worn off, a sterile 5 cm., 22 gage needle was inserted into the peritoneal cavity in the left lower quadrant of the abdomen at the level of the lower border of the omentum. Despite manipulation of the needle in all directions, no omental movements were noted during a period of some fifteen minutes.

Three months later, 1.5 cc. of a fresh virulent culture of B. coli containing about 5,000,000,000 organisms was injected into the peritoneal cavity in the left lower quadrant of the abdomen. Fluoroscopic examination twenty-four hours later showed no change in the position of the leaded silk.

Exploratory laparotomy performed six weeks after the implantation of bacteria showed the omentum to be completely free of adhesions. The leaded silk was encapsulated by the omentum, which was only slightly thickened. At the site of the injection of B. coli, there were a few fine adhesions between the serosa of the sigmoid colon and the parietal peritoneum of the lateral wall of the abdomen.

EXPERIMENT 3.—The dog was a tan and white female mongrel and weighed 12.3 Kg. With the dog under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midepigastric incision was made, and a rather

fatty omentum was delivered into the wound. Silver brain clips were buried in the free edges of the omentum in the right, left and central portions, which measured, respectively, 12, 7 and 14.5 cm. in length from the greater curvature of the stomach. The omentum was replaced, and the abdomen was closed in layers.

After three weeks, fluoroscopic maneuvers similar to those in experiments 1 and 2 were performed with identical results. The great omentum was seen to move only as the result of vigorous peristalsis induced by the injection of prostigmine methylsulfate.

Similarly, the injection of 5,000,000,000 virulent B. coli failed to produce any noticeable response within twenty-four hours. Exploratory laparotomy one month later showed slight induration of the omentum about the clips but no peritoneal or omental adhesions.

EXPERIMENT 4.—The dog was a brown female mongrel and weighed 10 Kg. With the dog under anesthesia induced with the intravenous administration of soluble pentobarbital, a high midepigastric incision 4 cm. long was made, and a slightly fatty omentum was brought out of the wound. Silver brain clips were buried in the right, left and central extremities of the omentum, 16, 10 and 17 cm., respectively, from the greater curvature of the stomach. The omentum was carefully reposited, and the abdomen was sutured in layers.

Three weeks later, fluoroscopic procedures similar to those in the other 3 experiments were conducted, and like observations were noted. Vomiting, defecation and the insertion of a sterile needle into the peritoneal cavity did not induce change in the position of the omentum. On the other hand, the vigorous peristalsis brought on by prostigmine methylsulfate produced definite lateral and longitudinal excursions of the omentum.

The injection of 5,000,000,000 virulent B. coli into the peritoneal cavity showed no evidence at fluoroscopy of having stimulated omental movement or change in position. Five weeks later, exploratory laparotomy was performed and revealed no omental adhesions. A few fine fibrous adhesions between the appendices epiploicae of the sigmoid flexure of the colon and the parietal peritoneum were found at the site of the previous inoculation of bacteria.

COMMENT

Normal conditions were simulated closely in all 4 experiments. The clips and the opaque thread buried in the omentum were light and small so that the factor of inertia was obviated. At subsequent laparotomy, the inflammatory reaction around the buried materials was found to be negligible. As no adhesions involving the great omentum developed, we were therefore assured that those movements which were seen were actually those of the unhampered omentum. The clips and the thread were clearly visible under the fluoroscope, and it was easy to follow their excursions.

In all instances, respiration caused longitudinal movement of the omentum over a distance of approximately 1 cm. These movements were synchronous with respiration, the omentum descending with inspiration and ascending with expiration. On repeated fluoroscopic

examination of the 4 animals in the resting state, no intrinsic lateral, longitudinal or axial omental movements other than those caused by respiration were seen.

The introduction of a needle at a site within easy reach of the omentum and its manipulation within the peritoneal cavity produced no response during a period of some fifteen minutes. This negative finding was particularly significant to us, for if the omentum was really endowed with active "intelligence," one might expect it to respond immediately to such a stimulus. This leads us to believe that the encapsulation of the foreign body which occurs after a few days is purely passive in character and is not dependent on any active intrinsic property of the omentum.

The physiologic processes of vomiting and defecation did not induce omental motility. On the other hand, hyperperistalsis induced by the injection of prostigmine methylsulfate resulted in definite lateral and longitudinal changes in the position of the omentum. These excursions measured anywhere from 3 to 6 cm. in extent. The conclusion to be drawn from these observations is that the omentum is moved passively by exaggerated peristaltic activity of the underlying coils of bowel. While vomiting and defecation are also concerned with peristalsis, in these processes the intestinal contractions are not vigorous enough to impart their effects to the overlying omentum.

The peritoneum was irritated by implanting large doses of virulent B. coli at a site within reach of the great omentum. Generalized peritonitis did not develop in any animal, even though the dose of organisms was greater than that reported by Coller, Ransom and Rife[12] as lethal for normal dogs. The peritoneum apparently handled the insult locally, for the omentum did not respond within an observation period of twenty-four hours. Fluoroscopic examination before and twenty-four hours after the implantation of bacteria revealed no changes in the position of the omentum. At subsequent laparotomy several weeks later, the omentum lay free within the peritoneal cavity and showed no evidence by adhesions or by changes in location of having taken part in the defense against the bacterial invasion. Adhesions of the bowel to the wall of the abdomen were present in 2 dogs at the sites of the implantation of bacteria. This suggests the conclusions that the peritoneum handles most insults locally and that perhaps the omentum becomes involved only by contiguity or by situations in which the peritoneum is overwhelmed and is unable to combat the infection alone.

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12. Coller, F. A.; Ransom, H. K., and Rife, C. S.: Reactions of Peritoneum to Trauma and Infection: Further Experimental Studies, Arch. Surg. **39**:761 (Nov.) 1939.

SUMMARY AND CONCLUSIONS

The great omentum of the dog has no active intrinsic motile power. Slight longitudinal excursions of the omentum are caused by respiration. Vomiting and defecation do not produce changes in the position of the omentum. Hyperperistalsis produces marked longitudinal and lateral movements of the omentum. Movements of the great omentum are passive and are dependent on the activity of the underlying bowel. There is no immediate response of the omentum to the insertion of a foreign body into the peritoneal cavity. The peritoneum of the bowel and the wall of the abdomen handled the intraperitoneal injection of several billion virulent B. coli locally. Although the site of injection was within easy reach of the great omentum, it did not move to the vicinity, nor did it take part in localizing the process.

PREGANGLIONIC COMPONENTS OF THE FIRST THORACIC NERVE

THEIR ROLE IN THE SYMPATHETIC INNERVATION OF THE UPPER EXTREMITY

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AND
JOHN B. DILLON, M.S.
ST. LOUIS

Operative procedures designed to effect functional sympathetic denervation of the upper extremities have occupied the attention of surgeons and experimental investigators. Clinical reports of cases in which operations for sympathetic denervation of the upper extremity have been carried out in the treatment of peripheral vascular disease indicate a relatively high percentage of failure to obtain complete functional elimination of the vasomotor and sudomotor nerves. This is due in part to anatomic variations. On the other hand, some of the operative procedures which have been outlined are not based on complete knowledge of the anatomic relations of the nerves in question and are not sufficiently extensive to interrupt all the sympathetic pathways leading into the upper extremity.

The gray communicating rami through which sympathetic fibers join the brachial plexus are derived mainly from the cervicothoracic and the middle cervical sympathetic ganglions. These ganglions receive preganglionic fibers via the white communicating rami of the first and lower thoracic nerves. It does not follow, without further proof, that all these white rami convey preganglionic fibers which effect synaptic connections with ganglion cells the axons of which extend into the upper extremity. The results reported by various investigators have not led to the same conclusions regarding the sources of the preganglionic fibers involved in the sympathetic innervation of the upper extremity.

On the basis of the data obtained in a series of anatomic and physiologic experiments carried out on cats and dogs, Kuntz, Alexander and Furcolo [1] concluded that the white communicating rami of the first and lower thoracic nerves include preganglionic fibers which effect synaptic connections with ganglion cells involved in the sympathetic innervation of the upper extremity. Preganglionic components of the

From the departments of microanatomy and physiology of the St. Louis University School of Medicine.

1. Kuntz, A.; Alexander, W. F., and Furcolo, C. L.: Complete Sympathetic Denervation of the Upper Extremity, Ann. Surg. **107**:25-31, 1938.

first and lower thoracic nerves also extend upward in the cervical portion of the sympathetic trunk. According to their findings, axons of ganglion cells in the cervicothoracic (stellate) ganglion, which are synaptically related to preganglionic components of the first thoracic nerve, are relatively widely distributed in the upper extremity, particularly in the distal portions, both to the vascular musculature and to the sweat glands.

In a recent investigation of the sympathetic preganglionic outflow to the limbs of monkeys, Sheehan and Marrazzi [2] used the action potential records obtained from peripheral nerves on stimulation of the ventral nerve roots as criteria of the conduction of impulses through sympathetic fibers. On the basis of their findings, they reported that in the rhesus monkey the preganglionic outflow to the upper extremity is limited to the fourth to the eighth thoracic nerves inclusive, with the major outflow in the fifth, sixth and seventh. They found no evidence of preganglionic fibers to the upper extremity in the first, second or third thoracic nerves. Although they presented no new data bearing on the preganglionic sympathetic outflow to the upper extremity in cats and dogs, they expressed the opinion that the results of faradic stimulation of the ventral roots of the upper thoracic nerves reported by Kuntz, Alexander and Furcolo may have been vitiated by unobserved spread of the stimulating current.

In view of the importance of more exact knowledge regarding the distribution of the preganglionic components of the upper thoracic nerves, it has seemed desirable to carry out a further study with the aid of a technic which is not subject to the errors which may result whenever ventral nerve roots are stimulated directly. The photoelectric plethysmograph affords such a method since it provides a convenient means of recording changes in the amplitude of the volume pulse wave due to reflex vasoconstrictor stimulation, particularly in the distal segments of the digits. This apparatus and its application in investigations involving changes in the peripheral circulation have been amply described by Hertzman and Dillon.[3]

METHOD

In the present series of experiments, carried out on cats and rhesus monkeys, the volume pulse wave in the toe or the finger pads was recorded while the afferent stimulus (ice or faradic stimulation) was applied to one of the lower extremities. With the animals under anesthesia induced with soluble pentobarbital, records were taken before operation, after extirpation of the second and third

2. Sheehan, D., and Marrazzi, A. S.: Sympathetic Preganglionic Outflow to Limbs of Monkeys, J. Neurophysiol. **4**:68-79, 1941.

3. Hertzman, A. B., and Dillon, J. B.: Distinction Between Arterial, Venous and Flow Components in Photoelectric Plethysmography in Man, Am. J. Physiol. **130**:177-185, 1940.

thoracic segments of the sympathetic trunk, leaving the first thoracic nerve with its white communicating ramus and the cervicothoracic ganglion with its gray communicating rami intact, and after extirpation of the cervicothoracic ganglion in addition to the second and third thoracic segments of the sympathetic trunk. The records after operation were never taken on the day on which the operation was carried out but always after ample time had elapsed to permit of recovery from the effects of operative trauma or shock.

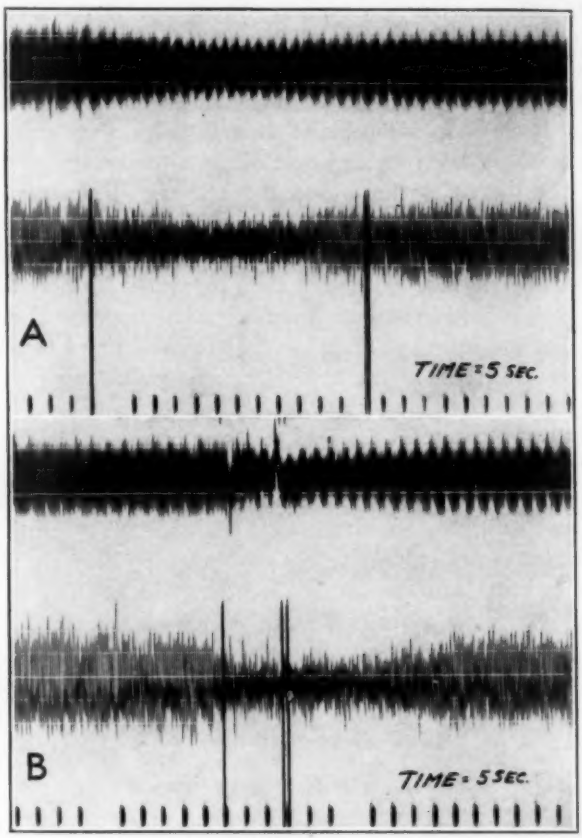

Fig. 1.—Photoelectric plethysmographic records from toe pads of the upper extremity of a cat under anesthesia induced with soluble pentobarbital made after unilateral extirpation of the second and third thoracic segments of the sympathetic trunk, leaving the cervicothoracic ganglion and its connections with the first thoracic nerve and the brachial plexus intact: *A*, upper record, from the side on which operation was done; lower record, from the other side. The stimulus was ice applied to the hind feet. *B*, upper record, from the side on which operation was done; lower record, from the other side. The stimulus was faradic stimulation in the femoral region. Stimulation was begun at the first marker and discontinued at the second.

RESULTS

In both cats and monkeys, application of ice to the soles of the hind feet or mild faradic stimulation of the femoral nerve elicited marked vasoconstriction, as indicated by the volume pulse wave record (figs. 1 and 3 *A*), in the digits of the upper extremity in the intact animal. In animals which had been subjected to extirpation of the second and third thoracic segments of the sympathetic trunk, leaving the first thoracic nerve and the cervicothoracic ganglion with its communicating rami intact, application of ice to the soles of the hind feet sometimes, and faradic stimulation of the femoral nerve always, elicited vasoconstriction in the digits of the upper extremity on the side of the operation

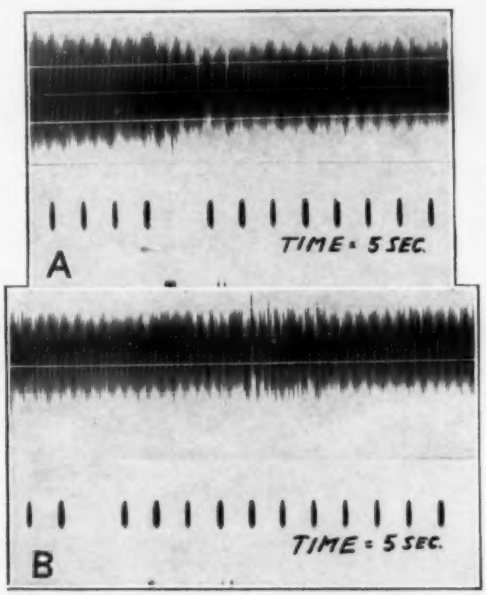

Fig. 2.—Photoelectric plethysmographic records from toe pads of the upper extremity of a cat under anesthesia induced with soluble pentobarbital: *A*, following extirpation of the second and third thoracic segments of the sympathetic trunk; *B*, following extirpation of the cervicothoracic ganglion after removal of the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the first marker and discontinued at the second.

(figs. 1, 2 *A* and 3 *B*). The change in the amplitude of the volume pulse wave, elicited by the stimulation employed, following extirpation of the second and third thoracic segments of the sympathetic trunk was less marked than that elicited in the intact animals, but always unmistakable. After extirpation of the cervicothoracic ganglion in animals which had previously been subjected to extirpation of the second and third thoracic segments of the sympathetic trunk, the same afferent stimulation usually

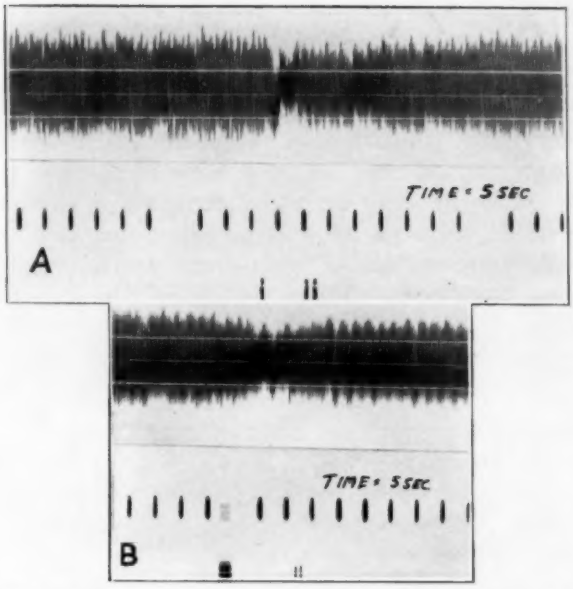

Fig. 3.—Photoelectric plethysmographic records from finger pads of a rhesus monkey under anesthesia induced with soluble pentobarbital: *A*, before operation; *B*, after extirpation of the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the first marker and discontinued at the second.

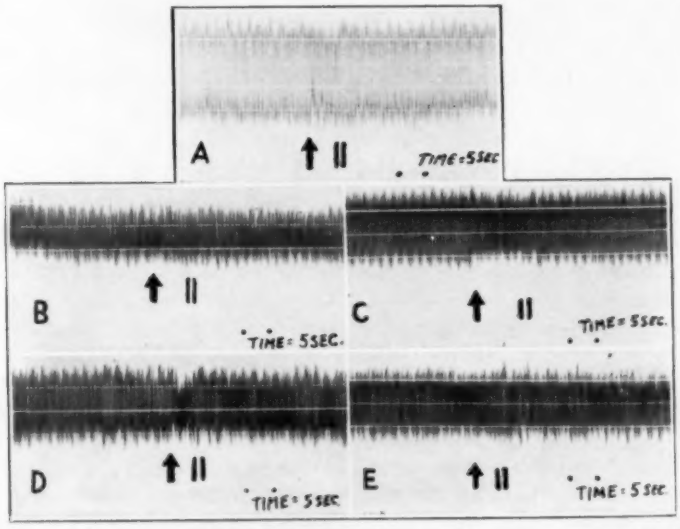

Fig. 4.—Photoelectric plethysmographic records from pads of all the digits of the upper extremity of a rhesus monkey under anesthesia induced with soluble pentobarbital following extirpation of the cervicothoracic ganglion with the second and third thoracic segments of the sympathetic trunk. Faradic stimulation in the femoral region was begun at the arrow and discontinued at the second marker. *A*, thumb; *B*, second digit; *C*, third digit; *D*, fourth digit; *E*, fifth digit.

failed to elicit any change in the volume pulse wave in the affected extremity (figs. 2 *B*, and 4 *A*, *B* and *E*). In a few instances, particularly in the monkey, it was possible to elicit a slight degree of reflex vasoconstriction (fig. 4 *C* and *D*), probably due to the presence of sympathetic fibers which join the brachial plexus from the nerves in the vertebral canal, which had not been interrupted.

COMMENT

The data obtained in the present series of experiments prove conclusivcly that reflex vasoconstriction in the digits of the upper extremity may be elicited after section of all preganglionic fibers below the first thoracic nerve which are involved in the sympathetic innervation of the upper extremity. Preganglionic components of the first thoracic nerve, consequently, must effect synaptic connections with sympathetic ganglion cells the axons of which extend into the upper extremity.

The operative procedure of extirpation of the second and third thoracic segments of the sympathetic trunk, as carried out, insures interruption of all preganglionic components of the second and third thoracic nerves and all preganglionic and postganglionic fibers which ascend in the sympathetic trunk from levels below the third thoracic segment. Care also was taken to interrupt any rami extending from the third thoracic nerve to the second or from the second to the first if such rami were present. The only efferent pathway through which vasoconstrictor impulses could reach the digits of the upper extremity following this operation, with the possible exception of a few sympathetic fibers which ascend in the vertebral canal and join the brachial plexus,[4] must include preganglionic components of the first thoracic nerve.

It is not without interest that in certain instances after extirpation of the cervicothoracic ganglion in animals in which the second and third thoracic segments of the sympathetic trunk had already been removed, as illustrated in fig. 4, *C* and *D*, afferent stimulation in a lower extremity resulted in slight vasoconstriction in certain of the digits but not in others. This result probably can be explained most satisfactorily on the assumption that the efferent impulses in question were conducted by sympathetic fibers which arise below the third thoracic segment, ascend in the vertebral canal and join the lower cervical and first thoracic nerves. Since but few of these fibers reach the upper extremity, they probably were represented in certain of the digits and not in the others.

The results of the present series of experiments support the assumption that the role of preganglionic components of the first thoracic nerve

4. Van Buskirk, C.: The Nerves in the Vertebral Canal and Their Relation to the Sympathetic Innervation of the Upper Extremities, Arch. Surg. **43**:427-432 (Sept.) 1941.

in the sympathetic innervation of the upper extremity is not unimportant and is comparable in the cat and the monkey. If the conditions in man may be regarded as comparable to those in the monkey with respect to the preganglionic components of the first thoracic nerve, it is evident that complete sympathetic denervation of the upper extremity cannot be accomplished by any operative procedure which leaves the cervicothoracic sympathetic ganglion with its gray communicating rami intact and does not interrupt the preganglionic components of the first thoracic nerve.

SUMMARY

In cats and rhesus monkeys, reflex vasoconstriction in the digits of the upper extremity has been demonstrated following extirpation of the second and third thoracic segments of the sympathetic trunk. The first thoracic nerve, consequently, must include preganglionic components which are involved in the sympathetic innervation of the upper extremity. The significance of this anatomic fact in relation to sympathetic denervation of the upper extremity is pointed out.